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Chapter 11: Factors That Impede Wound Healing

Rose L. Hamm; Tammy Luttrell

INTRODUCTION

CHAPTER OBJECTIVES

At the end of this chapter, the learner will be able to:

1. **Identify wounds that are not healing due to the influence of impeding factors.**
2. **Identify the impeding factors based on subjective and objective evaluations.**
3. **Select the tests necessary to confirm suspected impeding factors.**
4. **Adapt plan of care to minimize the effect of impeding factors on the wound healing process.**
5. **Educate patients and care givers on strategies to minimize or eliminate effects of impeding factors.**

Chapter 3, Examination and Evaluation of the Patient with a Wound, presented the two questions that need to be answered in order to successfully treat a patient with a wound: (1) Why does the patient have a wound? and (2) Why is the wound not healing? Once a wound diagnosis has been determined and standard care has been initiated, the wound should progress through the stages of wound healing discussed in Chapter 2, Healing Response in Acute and Chronic Wounds. When progress is not observed, the second question—Why is the wound not healing?—becomes even more imperative to answer. Sometimes the wound will respond initially and make measureable progress, then stall again for no apparent reason. This chapter focuses on those factors that are known to impede wound healing, some more obvious than others, and provides suggestions on how to identify and minimize the effect on the healing process. The factors are categorized into infection, medications, nutritional deficits, comorbidities, and extrinsic/psychosocial behaviors.

TABLE 11-1 provides laboratory values, always a good starting place for solving the conundrum, with normal values, trends that are typical when a patient does not have the normal healing response, and clinical presentations that accompany abnormal lab values.

CASE STUDY

INTRODUCTION

Mr RG is a 45-year-old male with a 3+ year history of a non-healing wound on the right anterior leg (**FIGURE 11-1**). His medical history includes the following:

- History of HIV for more than 15 years
- History of Kaposi sarcoma on the right anterior leg at the site of the current wound, treated with radiation and chemotherapy (doxol or doxorubicin)
- History of recurrent cellulitis, treated with both IV vancomycin and oral Xyvox

FIGURE 11-1

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Case study at the time of initial evaluation Non-healing wound on the lower extremity of a patient with multiple factors that impede wound healing.

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His HIV status is controlled with medication; he has an undetectable viral load and a low white count (≤3).

DISCUSSION QUESTIONS

1. What subjective information is needed to determine the factors that have prevented this wound from healing?
2. What questions would be helpful in obtaining this information?
3. What tests and measures are indicated in order to establish a plan of care?

TABLE 11-1

Laboratory Values with Implications for Wound Healing

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Laboratory Test	Normal Range	Values Affecting Wound Healing	Clinical Presentation
CBC			
WBC	4.5–11 × 10^3/mm^3	Increased Decreased	Signs of infection, inflammation, necrosis, trauma, or stress Failure to initiate immune response against bacteria
RBC	M 4.5–5.5 × 10^6/mm^3 F 4.1–4.9 × 10^6/mm^3	Decreased	Pale or anemic granulation or failure to progress
Hemoglobin	M 13.5–18 g/dL F 12–15 g/dL	Decreased Increased	Pale or anemic granulation or failure to progress Failure to progress (patient may show signs of congestive heart failure or COPD)
Hematocrit	M 37–50% F 36–46%	Decreased Increased	Pale or anemic granulation or failure to progress Signs of thrombi or emboli
Platelet count	150–400 × 10^3/mm^3	Decreased Increased	Bleeds easily, fatigue Signs of infection or inflammation
AUTOMATED DIFFERENTIAL			
Neutrophil rel	57–67% of leukocyte count	Increased	Bacterial infection Chronic inflammation
Lymphocyte rel	25–33% of leukocyte count	Increased Decreased	Signs of bacterial infection Opportunistic infections
Monocyte rel	3–7% of leukocyte count	Increased	Tissue injury Early healing response
Eosinophil rel	1–4% of leukocyte count	Increased Decreased (with corticosteroid use)	Allergic reaction Parasitic infection Delayed inflammatory response
Basophil rel	0–0.75% of leukocyte count	Increased	Allergic reaction
Neutrophil abs	4,300–10,000 cells/mm^3	Increased	Signs of infection
Lymphocyte abs	2,500–3,300 cells/mm^3 2,000–2,500/µL	Increased Decreased	Signs of bacterial infection Opportunistic infections
Monocyte abs			
Eosinophil abs			
Basophil abs	0–1,000 cells/mm^3	Increased	Allergic reaction

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COAGULATION STUDIES			
PT (prothrombin time)	12.3–14.2 seconds	Increased (>2.5 × reference range)	Bleeds easily
PTT (partial thromboplastin time)	25–34 seconds		
INR	Normal 0.9–1.1 Therapeutic range 2–3 Mechanical heart valves 2.5–3.5	Elevated	Bleeds easily Skin bruising
ROUTINE CHEMISTRY			
Sodium	135–145 mEq/L		
Potassium	3.5–5.3 mEq/L		
Chloride	95–105 mEq/L		
CO_2	22–29 mEq/L 35–45 mmHg (arterial)		
Glucose	70–115 mg/dL	Decreased (<70) Increased (>200)	Headache, dizziness, altered mental status, malaise Arrested healing processed Signs of infection Increased risk of abscess formation
Calcium	8.8–10.5 mg/dL		
Phosphate	2.5–5.0 mg/dL		
BUN	7–18 mg/dL	Increased (renal failure) Decreased (liver failure)	Edema Poor healing Jaundiced skin Yellow fluids
Creatinine	0.1–1.2 mg/dL	Increased (renal failure) Decreased	Edema Decreased lean body mass
Albumin	3.5–5.5 g/dL	Decreased Increased	Lack of granulation tissue Bilateral edema Muscle wasting Signs of dehydration
Prealbumin level	15–36 mg/dL	Decreased	Poor wound healing Lack of granulation formation
Globulin	2.5–3.5 g/dL		

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Fibrinogen	200–400 mg/dL		
A/G ratio	1.5:1–2.5:1	Decreased (liver damage) Increased (iron deficiency)	
Bilirubin total	0.1–1.0 mg/dL	Increased	Yellow wound fluids Jaundiced skin
Alkaline phosphate	30–85 U/L		
OTHERS			
Hemoglobin A1C	4–6%	Increased	Delayed healing
C-reactive protein (CRP)	0–1.0 mg/dL or <10 mg/L	Increased	Inflammation Infection
Retinal binding protein	10 mg/L 0.002 g/kg body wt	Increased	Delayed healing due to protein deficits
Magnesium	1.5–2.5 mEq/L		
Phosphorus	2.5–4.5 mg/dL		
Iron		Decreased Increased	Lack of granulation Hemochromatosis
Ferritin		Decreased Increased	Anemic granulation Lack of granulation Hemosiderosis
Transferrin	204–360 µg/dL <0.1 g/kg body wt	Decreased Increased	Delayed wound healing due to protein deficits Iron deficiency
Zinc	>60 µg/dL	Decreased	Delayed wound healing Lack of epithelialization Bullous—pustular dermatitis Intercurrent infections Weight loss
MICROBIOLOGY			
Wound culture	Negative	Positive	Poor wound healing Wound degradation
Blood culture	Negative	Positive	Systemic signs of infection

Data from Goodman CC, Fuller KS, Boissonnault WG. *Pathology: Implications for the Physical Therapist*. 2nd ed. Philadelphia, PA: Saunders; 2003. Huether SE, McCance KL. *Understanding Pathophysiology*. 4th ed. St Louis, MO: Mosby; 2008.

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INFECTIONS

Definition of Terms

Pathogens, defined as any microorganism that can cause disease in its host, can either damage or infect any wound tissue, or they can adhere to and colonize the wound surface. One distinguishing feature of pathogenic (vs nonpathogenic) microorganisms is their ability to evade the host innate and adaptive immune defenses. Pathogens have developed a variety of strategies to avoid immediate destruction by the host, including covering themselves in a thick polysaccharide capsule termed *biofilm*,[1,2] or in the case of mycobacterium (eg, *Mycobacterium leprae*, *Mycobacterium tuberculosis*), growing inside the macrophage phagosomes while inhibiting the phagosomal acidification and subsequent fusion with lysosomes.[3] Bactericidal agents (eg, toxic oxygen-derived products, nitric oxide, AMPs, and enzymes) are released by the phagocytic cells and are intended to render the invader harmless; however, these agents have consequences—they damage the surrounding host tissue and may potentiate the chronic proinflammatory state observed in chronic wounds (see **FIGURES 11-2** and **11-3**).

FIGURE 11-2

Infected wound Wound infected with *Staphylococcus aureus.* The bacteria are not visible; however, the signs of persistent periwound erythema, drainage, epidermal sloughing, and failure to heal are signs of infection. Pain and warmth are other signs of infection that may be present.

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FIGURE 11-3

Infected wound Biofilm, the polysaccharide covering produced on the surface of a wound by bacteria, may not be visible; however, the thick film on the surface of the toe wounds is an indication of possible infection. In this case, the wound culture was positive for MRSA.

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Just as the skin is known to have certain flora residing on the surface, so the wound bed has a variable amount of microbial presence that is defined as contaminated, colonized, critically colonized, or infected (see **TABLE 11-2**). The effect of the microbes on the wound bed is dependent on the type of bacteria, the number of colony-forming units (CFUs) per gram of tissue, and the host immune system. Colonization and critical colonization may respond to topical antimicrobials (see Chapter 13, Wound Dressings)[2]; infection and sepsis require that the patient receive systemic antibiotics specific to the invading microbe.

TABLE 11-2

Terms Defining the Presence of Bacteria on a Wound

Contaminated

- **Contamination**—presence of non-replicating bacteria on the wound surface without any effect upon the wound healing process
- **Colonization**—presence of replicating bacteria attached to the wound surface with no harm to the host and no effect on the wound healing process
- **Critical colonization**—presence of replicating bacteria on the wound surface with sufficient numbers to visibly affect the wound healing process
- **Infection**—presence of replicating bacteria that have invaded the surrounding tissue with visible effects in the wound healing process and in the periwound tissues. Clinical infection for most bacteria is defined as 10^5 CFUs/g of tissue
- **Sepsis**—presence of replicating bacteria that produces a whole-body inflammatory state termed systemic inflammatory response syndrome (SIRS)

Bacterial Infection

The innate immune response is initiated with the engagement of primary host cells and conserved bacterial components, defined as the repetitive arrays of carbohydrates, lipids, and proteins that are contained in the bacteria cell walls. These repetitive arrays are termed pathogen-associated molecular patterns (PAMPs) and the receptors that recognize them are termed pattern recognition receptors (PRRs). Host cells (eg, macrophages) constitutively express PRRs that recognize essential and highly conserved microbial components. The PRRs recognize the microbe by contact with its living extracellular components or its phagocytosed components after it has been ingested. Although the PRRs have a limited degree of specificity, they are specific enough to engage the host innate immune system.

Gram-positive bacteria carry a number of proinflammatory cell wall components including peptidoglycan (PGN), teichoic acid, lipoteichoic acid, and other surface proteins. Gram-negative organisms express an extremely potent proinflammatory lipopolysaccharide (LPS). As a result, the evolution of the host innate immune system includes separate and distinct, although sometimes overlapping, sets of sensors to detect the components of both gram-positive and gram-negative organisms. The detection of the organism then sets into motion a cascading proinflammatory response from

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resident macrophages and leukocytes.[1] Bacteria are further characterized as aerobic (needing oxygen to survive) and anaerobic (able to survive without oxygen), and can coexist in chronic wounds, especially if there is necrotic tissue present.[4] **TABLE 11-3** provides a list of bacteria most commonly found in chronic wounds.

TABLE 11-3

Microorganisms Most Commonly Present in Chronic Wounds

Aerobes (need oxygen to survive)

- *Acinetobacter baumannii*
- Coliforms
- *Enterococcus faecalis*
- Methicillin-resistant *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Streptococcus pyogenes*

Anaerobes (do not need oxygen to survive)

- *Bacteroides* spp
- *Fusobacterium* spp
- *Peptostreptococcus* spp
- *Porphyromonas* spp
- *Prevotella* spp
- *Veillonella* spp

Biofilms

Colonizing pathogens establish an attachment to the host epithelium or wound surface that is composed of an exopolymeric matrix of polysaccharides, proteins, and DNA synthesized by the bacteria.[4] The substance is adherent to the wound bed, providing an environment for the bacteria to live and replicate, and thus it is not easily removed by mechanical force or competing bacteria. Studies indicate that the first microorganism to establish host attachment has an advantage over subsequent colonizers even though competition of bacteria often occurs at the level of attachment to host receptors.[5] The biofilm can sometimes resemble a layer of slough on the wound surface, or it can be invisible (**FIGURE 11-4**). In order for the wound to progress from chronic to healing, the biofilm must be removed, preferably with sharp debridement as most antimicrobial dressings will not penetrate the biofilm to kill the bacteria although they can suppress biofilm formation.[2]

FIGURE 11-4

Biofilm on the wound surface Biofilm can appear as a thin, adhered yellow layer on the wound that is difficult to penetrate with antimicrobial dressings. Usually sharp debridement, in combination with contact low-frequency ultrasound or an iodine-based topical dressing, is required to remove the film and attached bacteria.

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Fungus Infections

Fungus infections are an increasing problem, especially among patients who are immunosuppressed or have transplants. Recent studies indicate that the fungal response to phagocytosis actively modulates the host immune cell function. Fungal pathogens avoid detection by masking PAMPs (such as cell wall carbohydrates), and by down-regulating the complement cascade. Once detected, various species of fungi actually interfere with phagocytosis and can repress production of antimicrobial substances like NO. Some fungi successfully replicate while inside the host macrophage. It is becoming readily apparent that fungi manipulate the host–pathogen interaction to their advantage (**FIGURE 11-5**).[6]

FIGURE 11-5

Fungal infection Fungal infections can occur under compression wraps if the skin becomes a supportive moist environment. Note the circular presentation of the infections, which has given some fungal infections the laymen's nomenclature of ringworm.

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In the wound care clinic, they are sometimes observed in conjunction with compression therapy, especially if using dressings and systems that stay in place up to 7 days. The moisture of both wound drainage and perspiration creates an environment where fungi thrive. The infection can usually be managed with a topical antifungal medication, adequate absorbent dressings to manage the wound fluid, and more frequent dressing changes.

Identification of an infected wound is not always easy for even the most astute clinician. The most common signs are persistent periwound erythema, drainage, epidermal sloughing, odor, and failure to respond to standard care. Friable granulation tissue in a previously progressing wound bed is another sign of infection. Specific to the diabetic foot ulcer, erythema that extends more than 2 cm from the edge of the wound is highly correlated with infection; and if the wound can be probed to bone, there is a possibility of osteomyelitis.[7] Accurate identification of any bacteria or fungi that is impeding wound healing is necessary for effective treatment, and effective treatment is necessary for wound healing to progress. A recent study found that swabs and biopsies yield the same culture results when taken from the same location, suggesting that biopsies are indicated only when needed for a pathological diagnosis, not for bacteria identification.[8]

MEDICATIONS

Steroids

Anti-inflammatory steroids, including glucocorticosteroids, are known to significantly affect many aspects of wound healing. When steroids have been part of the patient's medication regime prior to wounding, the elevated corticosteroid levels delay the appearance of inflammatory cells and fibroblasts; decrease the deposition of ground substances and collagen; and inhibit angiogenesis, wound contraction, and epithelial migration (**FIGURE 11-6A, B**).[9,10] The effect of steroid-mediated, delayed healing has been demonstrated to occur largely through the down-regulation of TGF-β and ILGF-1 and is apparent in all phases of wound healing. The effects of TGF-β on ECM formation are more profound than any other growth factor, and in the absence of TGF-β, matrix deposition and angiogenesis are impaired.[11] Specifically TGF-β is mitogenic for fibroblasts and stimulates the production of fibronectin and collagen. Insulin-like growth factor (ILGF-1) is a major regulator of wound healing. Wounds deprived of 90% of their IGFs demonstrate impairment in cell replication and deposition of collagen and a constitutive decrease in wound macrophage numbers. ILGF-1 also directly engages fibroblasts, endothelial and epithelial cells.[12,13]

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CASE STUDY

The following subjective information was obtained at the time of the evaluation:

- Works as a landscape artist
- Spends a lot of time standing and walking
- Is compliant with all medications, takes vitamins
- Works out at the gym 3–4 days a week
- Eats a healthy diet
- Has no history of smoking; occasional alcohol
- Has no history of drug abuse

The following objective information was obtained:

- Wound size: 2 × 2 cm
- Friable granulation tissue that bled very easily
- Periwound erythema
- Moderate serous drainage
- Moderate pitting edema with severe venous reflux
- 2–3/10 pain with touch or prolonged standing
- 3+ dorsalis pedis and posterior tibialis pulses
- No hair growth on the periwound skin

DISCUSSION QUESTIONS

1. What red flags indicate that critical colonization or infection may be present?
2. What risk factors does the patient have that make him susceptible to infection?
3. Are referrals to a medical specialist indicated? Which ones?

FIGURE 11-6

A. Wound on patient taking steroids The wound on the great toe of a patient who takes steroids for severe rheumatoid arthritis has impaired healing.

B. The wound after 10 days of treatment Debridement of necrotic tissue, low-frequency noncontact ultrasound, and antimicrobial dressings have decreased the periwound inflammation; however, the ability to move from inflammation to proliferation is slow.

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The wound healing trajectory is affected in several ways in patients who have been or are currently taking steroids. Decreased leukocyte infiltration, delayed insufficient inflammatory response to injury, and reduced autolysis of necrotic tissue are characteristics of a dampened response early in the healing process. The healing process and clearance of the debris and/or pathogen are inhibited secondary to decreased macrophage recruitment and proliferation. In the proliferative phase of healing the effects of steroids can be observed in the formation of less ground substance, decreased angiogenesis, and diminished fibroblast function, which directly decrease the amount of collagen synthesis. Fibroblasts do not differentiate into myofibroblasts, thus decreasing wound contraction and overall tensile strength. The effects of steroids on each phase of wound healing may lead to vulnerability for ulcer recurrence.[14]

Numerous studies have looked at the results of orthopedic surgery on patients (specifically with rheumatoid arthritis) who are on anti-inflammatory medications, either steroidal or disease-modifying antirheumatic drugs (DMARDs) such as methotrexate. A study on adverse events with craniovertebral junction fusion concluded that prednisone dosages <7.5 mg and/or methotrexate were safe with no effect on outcomes, whereas daily prednisone dosages >7.5 mg may impact clinical outcomes, as measured by the Nurick score.[15] Three studies on postoperative complications (surgical site infections and delayed wound healing) on patients taking DMARDs found no statistically significant difference in wound healing in those patients

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taking the medications.[16–18] In their review of perioperative use of DMARDs on patients undergoing plastic surgery, Tsai and Borah[19] suggest that in younger patients who have been placed on the medications recently, "it is reasonable to withhold therapy based on 3–5 half-lives of the specific agent," whereas in older patients with more advanced disease, discontinuing therapy must be carefully considered by the patient and the rheumatologist. However, a conflicting case study reported failure of a skin graft on a patient taking methotrexate.[20]

Two specific guidelines were issued by the British Society for Rheumatology: (1) methotrexate is unlikely to increase the risk of surgical complications if continued,[21] and (2) anti-TNFα drugs (infliximab, etanercept, adalimumab) "should be withheld for 2–4 weeks prior to major surgical procedures" and resumed when wound healing is satisfactory.[22] The decisions regarding steroid management for patients with chronic wounds demand careful consideration and observation from all the medical providers involved in their care.

Another potential side effect of long-term corticosteroid use that may affect wound healing is the development of drug-induced diabetes. This condition may not be diagnosed initially; therefore, if a patient receiving corticosteroid therapy has poor wound healing, monitoring blood glucose levels is advised. In addition, patients on steroids develop thin fragile skin that is at risk for skin tears (**FIGURE 11-7**).

FIGURE 11-7

Skin on patient taking steroids Patients on long-term steroid therapy have thin, fragile skin and tend to bruise easily, thus creating frequent superficial trauma wounds that are difficult to heal. Protection of the extremities with foam sleeves is beneficial, and meticulous wound care is required to prevent infection.

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Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat both autoimmune diseases and acute injuries because of their ability to decrease inflammation, prevent disease progression, and mitigate pain. (See **TABLE 11-4** for a list of commonly used NSAIDs.) These medications work by inhibiting both COX-1 and COX-2 enzymes, thereby decreasing the production of prostaglandins and leukotrienes.[23] The positive therapeutic effects of decreased production of prostaglandins are well known; however, the negative effects on wound healing are especially evident when given long-term and in higher doses.[24,25] The mechanisms through which wound healing may be impeded include the following:

- Decreased production of thromboxane A_2, which decreases platelet aggregation and increases the propensity for bleeding and hematoma formation, especially postoperatively[26]
- Inhibition of hyaluronic acid production with less granulation formation during the proliferative phase of healing

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- Decreased neutrophil migration to the wound site with increased risk of infection
- Decreased collagen synthesis with decreased tensile strength of new tissue

TABLE 11-4

Commonly Used NSAIDs That May Affect Wound Healing

Nonselective NSAIDs	Cyclooxygenase (COX)-2 Inhibitors	Disease-Modifying Antirheumatic Drugs (DMARDs)
Aspirin	Celecoxib	Azathioprine
Diclofenac (Voltaren)	Parecoxib	Penicillamine
Fenoprofen (Nalfon)	Rofecoxib	Methotrexate
Ibuprofen (Motrin, Rufen)	Valdecoxib	
Indomethacin (Indocin)		
Ketoprofen (Orudis)		
Meclofenamate (Meclofen, Meclomen)		
Naproxen (Anaprox, Naprosyn)		
Piroxicam (Feldene)		
Sulindac (Clinoril)		
Tolmetin (Tolectin)		

The results of several studies have led to the recommendation that NSAIDs be discontinued 1–4 weeks before surgery, depending on the half-life of the drug being taken by the patient, and some suggest that they should be withheld after surgery until the incision has healed.[14,27,28] Many of the studies are based on animal models and results are sometimes inconsistent, so the decision to discontinue their use before surgery needs to be weighed against the effects on the patient's pain and disease progression.

Some of the clinical signs that may be observed if the NSAIDs are affecting wound healing include failure to progress through inflammation to the proliferative phase, tissue that bleeds easily, poor-quality granulation tissue that will not support re-epithelialization, tendency to develop infections, and vulnerability to break down during the remodeling phase (**FIGURE 11-8**). Patients who are taking NSAIDs for pain relief and not for anti-inflammatory effects may have better healing by substituting acetaminophen, especially if the NSAID dosage is high. If patients are on high doses of any anti-inflammatory medications, it is advised that they be tapered off in order to avoid side effects of sudden withdrawal.

FIGURE 11-8

Stalled wound on patient who is taking NSAIDs The venous wound is clean and granulating; however, it has stalled and is not epithelializing. The patient, who had initially reported only medication for hypertension, told the therapist she was taking 800 mg of ibuprofen each day. Medications were discussed with her primary care physician; she was started pentoxifylline (vasodilator), discontinued ibuprofen, and changed hypertension medications. Within a week the wound had signs of epithelial migration at the edges.

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Anticoagulants

Anticoagulants (eg, warfarin, apixaban, rivaroxaban, and dabigatran) inhibit the coagulation cascade and thereby may prevent fibrin deposition and delay the healing process.[24,29] Two patient populations that were found to have significantly higher rates of postoperative wound and bleeding complications were women who received anticoagulation during pregnancy and required Cesarean delivery[30] and patients who were female and/or received oral anticoagulation and had lower extremity bypass surgery for critical limb ischemia. This does not undermine the importance of continuing anticoagulation therapy for those patients who require it for cardiac or thrombosis reasons. For any patient undergoing surgery and on anticoagulation therapy, the decision to continue medication during the perioperative period requires careful consultation between the surgeon and the prescribing physician to consider benefits and potential complications.

Cutaneous reactions to anticoagulation that have been reported are heparin-induced bullous hemorrhagic dermatosis, hematomas, ecchymoses, erythematous plaques, nodules, contact dermatitis, and urticarial,[31] as well as warfarin-induced skin necrosis (**FIGURE 11-9**). Although these conditions are rare, they are differential diagnoses to be ruled out in patients who develop skin necrosis, especially within 2 weeks of initiating therapy.[32]

FIGURE 11-9

Coumadin-induced skin necrosis Patient with warfarin- or Coumadin-induced skin necrosis on the posterior lower leg. Treatment included discontinuing warfarin, sharp debridement, and moist wound healing.

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Antirejection Medications

The hallmark of successful organ transplantation is suppressing the immune system so that the host does not activate the immune cells to a level sufficient to reject the allograft. **TABLE 11-5** provides a list of commonly used antirejection medications; most of which act by interfering with "discrete sites in the T- and B-cell cascades."[33] Specifically, the actions include inhibition of cytokine transcription, inhibition of nucleotide synthesis, inhibition of growth factor signal transduction, inhibition of the stimulation of T-cell interleukin (IL)-2 receptor sites, and diminished chemotaxis.[33,34] In addition, the effects of the corticosteroids include decreased counts of lymphocytes, monocytes (thus decreased macrophages), and basophils while increasing the number of senescent cells.[35] These altered cellular functions are known to impede wound healing, resulting in frequent dehiscence of the transplant surgical incision (**FIGURE 11-10**).

FIGURE 11-10

Surgical incision on a transplant patient The patient on antirejection medications (Prednisone and Cellcept) after liver transplant. Note the poor epithelial bridging of the approximated edges and the opening at the right side of the incision, indicating poor healing of the subcutaneous tissue with tunneling under the incision. The wound may require surgical I&D and negative pressure therapy to promote healing and prevent infection.

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TABLE 11-5

Antirejection Medications Used for Organ Transplantation

Azathioprine (AZA, *Imuran*)

Corticosteroids

- Primary endogenous glucocorticoid
- Cortisol
- Prednisone
- Methylprednisolone

Cyclosporine (CsA)

Tacrolimus (Prograf)

Mycophenolate mofetil (Cellcept)

Sirolimus (SRL, *Rapamune*)

Polyclonal antibodies

- Thymoglobulin
- Atgam

Monoclonal antibodies (OKT3)

- Daclizumab (Xanapax)
- Basiliximab (Simulect)

Calcineurin inhibitor (CI)

- CsA (Sandimmune, Neoral, and SangCya)

Mycophenolate mofetil (MMF)

Data from Lake DF, Briggs AD, Akporiaye ET. Immunopharmacology. In: Katzung BG, Masters SB, Trevor AJ, eds. *Basic & Clinical Pharmacology*. 12th ed. New York, NY: McGraw-Hill; 2012:chap 55. Available at: http://www.accessmedicine.com.ezproxy.cihe.edu.hk/content.aspx?aID=55831418. Accessed May 3, 2013.

Acute adverse effects of the antirejection medications may include increased risk of infection; nausea, vomiting, and diarrhea; and loss of appetite, all of which result in a diminished nutritional state with subsequent insufficient calories, proteins, and vitamins needed for incisional healing (**FIGURE**

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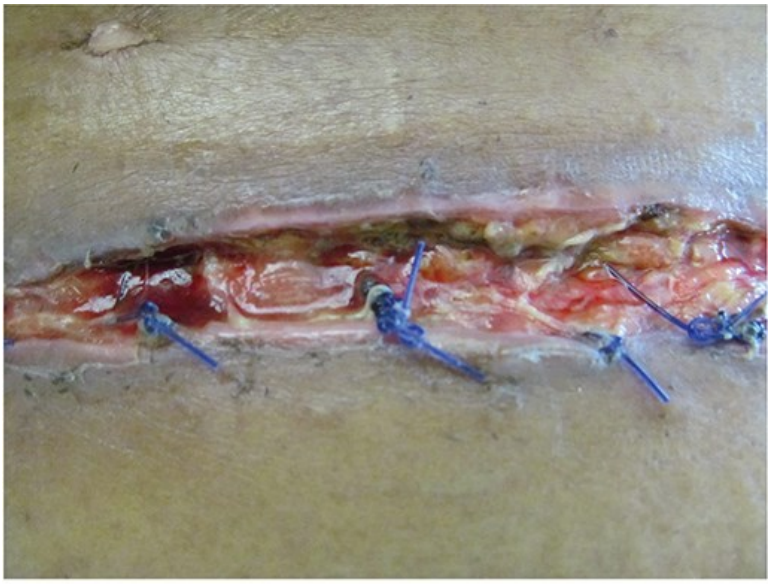
11-11).

FIGURE 11-11

Close view of surgical wound Evidence of protein deficiency is visible in the poor quality of the tissue in this surgical incision, including lack of granulation tissue, slough, rolled edges, and extrusion of the deep sutures, which are acting as a foreign body.



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Because antirejection medications are required for the life of the recipient, the effects on wound healing are long term and may result in chronic wounds. This is especially a problem if the patient develops drug-induced diabetes. Another long-term effect of the medications is a significantly higher rate of aggressive squamous cell carcinoma (SCC), a malignant skin cancer linked to the increased number of senescent cells,[35] and an oxidative environment.[36,37] Careful skin inspections are advised in order to detect SCC in the early stages and to increase survival rates.

COMORBIDITIES

Diabetes

Diabetes has multiple inhibitory effects on wound healing, including neuropathic, macrovascular, and microvascular changes, as well as altering cytokine and growth factor signaling. Regardless of the etiology of the wound (surgical, neuropathic, pressure, venous, arterial, acute, or chronic) the patient with diabetes or routinely uncontrolled blood glucose levels is at risk for delayed healing. At the cellular level, diabetes is associated with decreased PDGF receptor expression[38] on epithelial and endothelial cells, thereby altering the wound healing process at the initial phase of hemostasis. In addition, patients with diabetes exhibit a prolonged inflammatory phase attributed to the following:

CLINICAL CONSIDERATION

Even though they are acting as a foreign body, the blue sutures in a transplant incision cannot be removed because they are anchoring the deep fascial layers. Discussion with the surgeon will give the clinician direction on when and if sutures can be removed.

1. A disproportionate expression of vascular cell adhesion molecules by endothelial cells, which increases extravasation and inflammatory cell accumulation at the wound site.
2. The presence and increased infiltration of wound-activated macrophages (WAMs), which contribute to an increased and prolonged expression of inflammatory cytokines.[39,40]
3. Higher levels of neutrophil-formed extracellular traps (termed NETs[41]).

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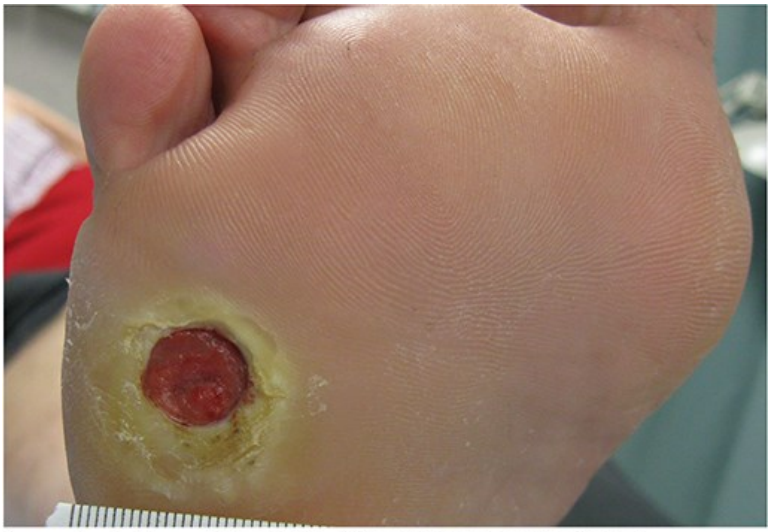
In the proliferative phase, diabetic wounds exhibit the following characteristics:

1. Increased accumulation of fibrotic ECM at wound edges results in stalled keratinocyte migration (**FIGURE 11-12**).[42]
2. Impaired fibroblast signaling (FGF—FGFR) further contributing to poor granulation tissue formation.[43,44]
3. Glycation of the ECM, which causes ECM instability and disrupts matrix assembly and interactions between collagen and proteoglycans.[45] The ECM instability is compounded by the fact that high glucose levels stimulate MMP production by fibroblasts, macrophages, and endothelial cells.[46]
4. Poor ECM maturation secondary to elevated MMPs and reactive oxygen species (ROS) from inflammatory cells. Early cell senescence diminishes the effectiveness of newly arriving progenitor cells and biases the local cellular environment toward one of oxidation and proinflammation.[35] The triad of early cell senescence, diminished cell proliferation, and impaired cellular migration escalates the challenge of wound healing in the patient with diabetes.[47]

FIGURE 11-12

Diabetic foot ulcer The heavy callus at the edge of a diabetic foot wound is a result of stalled keratinocyte migration and probable lack of total off-loading of the injured tissue.



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Finally, there is an altered sensitivity to VEGF[48] resulting in decreased endothelial progenitor cell numbers and recruitment in response to injured tissue, thereby leading to poor revascularization. The impact of these cell signaling defects by wound healing phase is illustrated in **FIGURE 11-13**.

FIGURE 11-13

Skin on the lower extremity of a patient with diabetes The brawny skin with multiple wounds is characteristic of poorly controlled diabetes, especially if the patient has renal failure. The punctuate appearance is a result of poor vascularization of the injured tissue.

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The American Diabetes Association (ADA) and the American College of Endocrinology (ACE) have established guidelines for blood glucose and hemoglobin A1C levels for patients with diabetes in order to minimize complications (**TABLE 11-6**). The ACE recommends that postoperative blood glucose levels be maintained at less than 180 mg/dL and further states that patients with hyperglycemia have higher infection rates.[49] Clinically, patients with diabetic foot ulcers who have A1C levels less than 7.1% have shorter healing times than those who have higher levels, and patients with higher A1C levels had more frequent ulcer recurrence.[50] Another review recommended that pre-surgical glucose levels be maintained in the 100–180 mg/dL range in order to prevent infection, decrease the risk of hypoglycemia, and prevent dehydration as a result of osmotic diuresis.[51]

TABLE 11-6

Recommendations for Glycemic Control for Patients with Diabetes

	Hemoglobin A1C	Fasting Plasma Glucose	Postprandial Plasma Glucose
ADA	<7%	90–130 mg/dL 5–7.2 mmol/L	<180 mg/dL <10 mmol/L
ACE	6.5%	<110 mg/dL <6.1 mmol/L	<140 mg/dL <7.8 mmol/L

Data from ADA—American Diabetes Association. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach. Available at: http://care.diabetesjournals.org/content/35/6/1364.full.pdf+html. Accessed August 29, 2018.

ACE—American College of Endocrinology. Clinical Practice Guidelines for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient—2013 Update. Available at: https://www.aace.com/files/publish-ahead-of-print-final-version.pdf. Accessed August 29, 2018.

An extensive review of diabetes and diabetic foot wounds is found in Chapter 7. However, the effect of diabetes, sometimes undiagnosed, on poor wound healing regardless of the wound etiology is a factor that always needs to be considered, especially if the patient has a known or suspected risk for diabetes or has a family history of diabetes.

Obesity

The health consequences of obesity include a range of negative outcomes, including cardiovascular disease,[52] diabetes,[53,54] physical limitations,[55] and decreased mobility.[56] Excess body weight influences the onset and progression of chronic illness through multiple pathways.[51] Adipose tissue is active,

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releasing nonesterified fatty acids, hormones (including leptin, glycerol, proinflammatory cytokines, eg, tumor necrosis factor-α), interleukin-6, and chemokines (including monocyte chemotactic protein-1), as well as other bioactive mediators.[57,58] In overweight or obese individuals, the increased number of adipocytes results in higher levels of all of these factors, thereby changing the regulation of basic physiologic processes at a systemic level,[57] and supposedly at the local level of the wound environment as well.

CASE STUDY

As treatment continued on the lower extremity wound of Mr RG, it was noted that the wound was granulated but not epithelializing. The patient had not reported diabetes at the time of evaluation, and did not have the bodybuild or diet to indicate he was high risk for diabetes. However, in exploring every possible cause of poor healing, in addition to the radiated tissue, the patient reported that his grandmother had diabetes with lower extremity complications that led to amputation. He agreed to have his fasting blood glucose levels tested and did indeed have type 2 diabetes. He initially tried to control his blood glucose levels with diet and exercise; however, when he developed other medical issues including a gastrointestinal bleed, he required oral medication.

DISCUSSION QUESTIONS

1. What are the mechanisms by which diabetes impedes wound healing?
2. What are the visible signs that would indicate a wound is not healing because of diabetes?
3. What risk factors does this patient have for diabetes?

There is now evidence that obesity also contributes to delayed wound healing by creating an aberrant low-level inflammatory state.[59] In addition, studies have shown that obese patients have higher risks for surgical site infections, wound dehiscence, and delayed wound healing.[60–62] This may be in part due to the decreased vascularity of adipose tissue with relative decreased oxygen tension, resulting in decreased collagen synthesis, decreased immunity to infection, overall decreased ability to support the processes of wound healing, and increased tissue necrosis (**FIGURE 11-14**).[63] The decreased vascularity may be inherent (with chronic low-grade inflammation and increased glucocorticoids that suppress angiogenesis) or acquired (as a result of surgical and trauma tissue injury that disrupts the adipose tissue); however, either mechanism can disrupt the normal healing process.[63] The heightened inflammatory state can also result in part from chronic venous insufficiency and thereby affect wound healing, especially in the lower extremities. The specific mechanisms involved in the chronic low-grade inflammatory process have been studied primarily in obese mice studies and have consistently shown increased proinflammatory cytokine production resulting from the activation of invariant natural killer T cells by the excess lipid.[63] Other inflammatory mediators that have been shown to increase with obesity include angiotensinogen, tumor necrosis factor alpha, leptin, interleukin 6, and transforming growth factor beta.[59,64] In addition, decreased adiponectin concentration (which occurs with obesity even though it is produced by adipocytes) impairs adequate profusion and wound epithelialization.[63] Other factors that may cause wounds or impede wound healing in the obese population are the prevalent comorbidities, non-adherence to treatment plans, poor nutrition, increased risk of friction/shear with resulting pressure ulcers, and confirmed infection.[65] Most strategies to address poor wound healing in the obese have concentrated on maintaining blood glucose levels, proper nutrition for optimal healing, preventing infections, and meticulous wound care. However, one animal study using obese mice suggests that physical exercise may help improve cutaneous healing in obese individuals.[59] Research on both cellular causes and interventions and holistic treatments such as exercise is still investigational but much needed, given the increased prevalence of obesity in our society.

FIGURE 11-14

Abdominal wound on postsurgical patient Obese patients are prone to poor healing of abdominal surgical wounds because of poor nutrition, prevalence of diabetes, poor vascularity of adipose tissue, and high risk of infection. These wounds frequently require surgical debridement, prolonged negative pressure wound therapy, and continued serial debridement and pulsed lavage with suction.

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Protein Energy Malnutrition

Healing a wound without protein is like building a house without bricks and lumber—amino acids are the building blocks needed for growth of new tissue, as was so exquisitely detailed in Chapter 2. Ingested proteins are metabolized into amino acids and peptides that serve as enzymes, hormones, cytokines, growth factors, and components of antibodies, all of which play a very important role in tissue maintenance and wound healing. Patient populations who are known to be at risk for protein energy malnutrition (PEM), defined as inadequate energy and protein intake to meet bodily demands, include the elderly,[66] HIV-positive patients,[67] and liver/cirrhosis patients (**FIGURE 11-15**).[68] **TABLE 11-7** lists the protein requirements for wound healing, and when these proteins are not available from daily nutrition, they are taken from the skeletal muscle stores.

FIGURE 11-15

Dehisced incision on a patient with liver transplant Patients who have liver cirrhosis are at risk for protein energy malnutrition, which impedes wound healing, as seen in this dehisced incision after a liver transplant. Healing is further compromised by the antirejection medications, which the patient has to take. Note the yellow jaundiced color of the skin, typical of patients with elevated bilirubin levels due to liver failure.

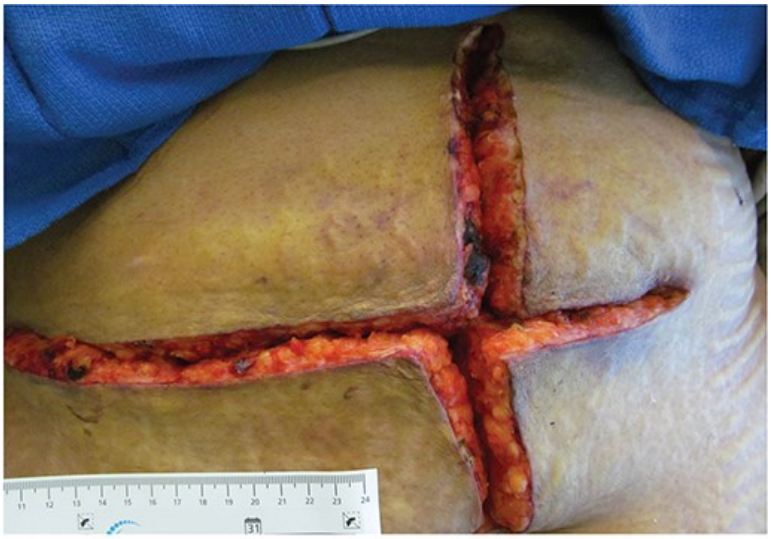

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TABLE 11-7

Nutritional Requirements for Wound Healing

	Calories[1]	Protein[2]
Normal (at rest)	20–25 kcal/kg/day (age dependent)	0.8 g/kg/day
		60–70 g
Postoperative/ill/injured	30–50% above normal	1.2–2 g/kg/day
Large open wounds, burns		2–2.5 g/kg/day
Malnourished	50% above normal	1.5g/kg/day plus anabolic agent[1]

[1]Data from Demling RH, Nutrition, anabolism, and the wound healing process: an overview. *ePlasty.* 2009;9:65–94.

[2]Huckleberry Y. Nutritional support and the surgical patient. *Am J Health Syst Pharm.* 2004;61(7):671–682, by permission of Oxford University Press.

The normal body is 75% lean body mass (protein and water) and 25% fat (the calorie reservoir). If there is loss of lean body mass, the host takes precedent over the wound and healing will not occur (**FIGURE 11-16**).[69] **TABLE 11-8** provides the relationship between loss of lean body mass and wound formation and/or healing. Laboratory values used to detect or measure PEM are given in **TABLE 11-1**, and include albumin, prealbumin, transferrin, and retinal binding protein. Albumin is commonly measured especially as an indicator for chronic malnutrition; however, it has the disadvantage of having a long half-life (20 days) and may not accurately reflect the protein substrates available for healing if the patient is acutely ill, dehydrated, or in hepatic or renal failure.[70] Advantages of prealbumin include the following: has a short half-life (48–72 hours), is not affected by dehydration or renal failure, does not increase with stress, decreases with sepsis and stress, and is easily monitored. Therefore, it is considered a more accurate reflection of a patient's nutritional status.[69] Transferrin is a glycoprotein that binds and transports iron, and its level decreases with inflammation and malnutrition. However, it is less reliable (may increase with iron deficiency) and more expensive, thus not used as frequently as the other measures.[71,72] Retinal binding protein levels have been shown to decrease with protein malnutrition and vitamin A deficiency, and it is especially sensitive in patients with acute stress, inflammation, and infection, as well as in women and children.[73]

FIGURE 11-16

Patient with loss of lean body mass Patients who have 30% loss of lean body mass are at high risk for developing pressure ulcers. Note the severe muscle atrophy and lack of soft tissue to protect the bony prominences, with resulting Stage I pressure ulcers on the scapula. Whether or not pressure ulcers on these patients are preventable remains controversial.

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TABLE 11-8

Loss of Lean Body Mass Relative to Wound Healing

% Loss of Total Lean Body Mass	Implication for Wound Healing
10%	Impaired immune response, increased risk of infection
20%	Impaired or delayed wound healing, increased risk of infection, thin skin
30%	No wound healing, increased incidence of pressure ulcers
40%	Death, usually from pneumonia

Used with permission from Demling RH. Nutrition, anabolism, and the wound healing process: an overview. *ePlasty.* 2009;9:65–94.

Recent literature discusses the limitations in using these values to determine malnutrition because the inflammatory process can affect these levels in almost all chronic conditions, terming the values “negative acute-phase reactants” and, thus, no longer valid to use alone as a basis for providing nutritional interventions.[74,75] In 2012 the Academy of Nutrition and Dietetics (Academy) and the American Society for Parenteral and Enteral Nutrition (ASPEN) released a joint consensus statement that proposes a three-pronged etiology-based definition of malnutrition (**TABLE 11-9**), as well as the following six characteristics for the diagnosis:

- insufficient energy intake
- weight loss
- loss of muscle mass
- loss of subcutaneous fat
- localized or generalized fluid accumulation that may sometimes mask weight loss
- diminished functional status as measured by hand-grip strength.[75]

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TABLE 11-9

Etiology-Based Definitions of Malnutrition

1. Malnutrition in the context of social or environmental circumstances (starvation-related malnutrition). May be pure starvation due to financial or social reasons or caused by anorexia nervosa.
2. Malnutrition in the context of acute illness or injury, such as organ failure, pancreatic cancer, rheumatoid arthritis, or sarcopenic obesity.
3. Malnutrition in the context of chronic illness, such as major infections, burns, trauma, or closed head injury.

Guidelines state that the presence of two or more of these criteria constitutes a diagnosis of malnutrition. Thus, one of the most important aspects of diagnosing malnutrition is the subjective patient history (including recent food intake, unintentional loss of body weight, medications), physical examination, and functional assessment.

CLINICAL CONSIDERATION

For very active patients, for example, runners, who are having difficulty with wound healing, assessing the caloric intake with the energy expenditures during exercise may be helpful, in which case limiting the exercise until wound healing is completed may be the solution.

Laboratory values for inflammation (C-reactive protein, white blood count, and blood glucose levels) can help determine if the malnutrition is due to starvation, chronic disease, or acute disease/injury.[75] Two other screening tools that have been published are the Canadian Nutrition Screening Tool and the MEAL Scale. The Canadian Tool asks the patient the following two questions:

1. Have you lost weight in the past 6 months without trying to lose this weight? (If the patient reports a weight loss but gained it back, consider it as no weight loss.)
2. Have you been eating less than usual for more than a week?

Two “yes” answers indicate malnutrition risk, and this was shown to be valid with or without considering the patient's body mass index. Validity testing of the Canadian Tool was performed on 1,015 patients admitted to 18 Canadian hospitals for more than 2 days.[76] Fulton et al.[77] looked at 18 factors thought to be associated with malnutrition and found only 4 to be statistically significant: presence of multiple wounds, eating less than usual, eating less than 3 meals per day, and a low activity level. Using this information, they developed the MEAL Scale (**TABLE 11-10**) for nutrition screening in the wound patient population.

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Table 11-10

The MEAL Scale for Nutrition Screening in the Wound Patient Population

Multiple wounds	Do you have >1 open wound?	
	0 1	No Yes
Eats <3 meals	How many meals, not including snacks, do you eat in a typical day?	
	0 1	≥3 meals ≤3 meals
Appetite loss	Thinking about your normal food intake, would you say you are eating about the same, more, or less than usual?	
	0 1	About the same or more than usual Less than usual
Level of activity	Thinking about your normal level of activity, how would you consider your activity level over the past month?	
	0 0 1 1 2	Normal Not quite normal, but able to do most things Not feeling up to most things, in bed or chair less than half the day Able to do little activity and spend most of the day in bed or chair Pretty much bedridden, rarely out of bed

Total points: 0–1, not at risk; 2–4, at risk.

Adapted from Fulton J, Evans B, Miller S, et al. Development of a nutrition screening tool for an outpatient wound center. *Adv Skin Wound Care*. 2016;29(3):136–142. Available at https://journals-lww-com.ezproxy.cihe.edu.hk/aswcjournal/Fulltext/2016/03000/Development_of_a_Nutrition_Screening_Tool_for_an.11.aspx.

The Mini Nutritional Assessment (MNA)® was developed by the Nestle Research Center and Toulouse University, France, for the older population but is also useful in other patient groups. The MNA® consists of 18 easily measurable items classified into the following 4 categories:

1. Anthropometric measurements (four questions on weight, height, and weight loss)
2. Dietary questionnaire (six questions related to number of meals, food and fluid intake, autonomy of feeding)
3. Global assessment (six questions related to lifestyle, medication, and mobility)
4. Subjective assessment (two questions on self-perception of health and nutrition)

Validation studies demonstrated the strong capacity of the MNA® to evaluate the nutritional status of older adults and had a strong correlation with biochemical parameters, especially albumin. The full tool with explanations for administering is available on their website https://www.mna-elderly.com/forms/mini/mna_mini_english.pdf.[78]

The macronutrients needed for wound healing include carbohydrates which stimulate insulin production and help in the anabolic process of wound healing, fats which supply additional calories, proteins which are needed for collagen synthesis and granulation formation, and fluids (particularly water) which maintains skin turgor and promotes tissue perfusion and oxygenation.[74] The micronutrients (including amino acids, vitamins, and minerals) are also vital to wound healing; however, the need for supplementation is less definitive. **TABLE 11-11** contains a list of micronutrients important for cellular function, survival, and thus for wound healing. These nutrients tend to be deficient during severe stress and with PEM and thus

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amplify stress, metabolic derangements, and catabolism.[68]

TABLE 11-11

Micronutrients Needed for Wound Healing

Vitamin A	Stimulant for onset of wound healing, epithelialization, and fibroblast deposition of collagen
Vitamin C	Cofactor for collagen synthesis, immunity, fatty acid metabolism
Copper	Cofactor for connective tissue production, collagen cross-linking, and cytochrome oxidase for energy production
Manganese	Cofactor for collagen and ground substance synthesis
Zinc	Cofactor for DNA, RNA, and polymerase for collagen and ground substance synthesis

Data from Demling RH. Nutrition, anabolism, and the wound healing process: an overview. *ePlasty.* 2009;9:65–94. Department of Surgery, Brigham and Women's Hospital, Boston, MA, and Burn and Wound Program, Health South Braintree Rehabilitation Hospital, Braintree, MA. The stress response to injury and infection: role of nutritional support. *Wounds.* 2000;12(1). Available at: http://www.medscape.com/viewarticle/407543. Accessed June 23, 2013.

Arginine is an amino acid used in the biosynthesis of protein, a necessary process for wound healing to occur. Benefits of arginine supplementation include increased collagen deposition, increased lymphocyte mitogenesis, increased production of growth hormone, and increased activation of T cells.[79] A study by Leigh et al.[80] of patients with pressure ulcers found that 4.5 g/day supplementation of arginine was sufficient to facilitate wound healing but must be given with adequate protein intake to be effective. Vitamins A, C, and D all play a role in the wound healing process, and deficits have been shown to impede the progression of the healing cascade.[81] Supplementation is recommended only if there are measured deficits with the following recommendations for amounts:

1. Vitamin A—10,000–15,000 IU/day administered in a short course of 10–14 days to prevent toxicity
2. Vitamin C—500–1,000 mg in divided doses for wound healing and 1–2 g/day for severe wounds, eg, extensive burns
3. Vitamin D—deficient in patients with venous ulcers and pressure ulcers; dosages not given[74]

The minerals which have been suggested as critical in wound healing, specifically in enzyme and metalloenzyme structure, include zinc, selenium, and iron. Zinc deficiency affects all phases of wound healing; however, supplementation is recommended only in the case of deficiency.[81] Recommended supplementation in the zinc-deficient patient range varies from 40 mg/day to 220 mg twice a day for 10–14 days, and must be carefully monitored because excessive zinc supplementation can interfere with the absorption of iron and copper.[74] Negative pressure wound therapy, particularly of open abdominal wounds, has been shown to significantly reduce the amounts of micronutrients; therefore, these patients need to be nutritionally monitored and supplements provided as needed.[82]

One of the most helpful questions to use in the subjective examination is “What did you have for breakfast this morning?” and “What did you have for dinner last night?” The answers can give useful insight into the patient's eating habits such as protein intake, caloric intake, and consumption of high-glycemic index foods (especially important for patients with pre- or diagnosed diabetes). Concerns that are raised as a result of the answers can be followed up with additional tests and measurements. Nutritional supplements are an integral part of treating patients who have PEM, and oral or enteral nutrition is preferred over parenteral nutrition.

In summary, all patients with non-healing wounds need to be screened for nutritional deficiencies. Any patient found at risk by a screening tool or who has other red flags that indicate inadequate nutrition may be a factor in poor healing capacity is advised to have further testing for specific deficits, counseling by a registered dietician, and supplements when deemed appropriate.[83]

Arterial Insufficiency

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A non-healing wound may be the first visible sign of undiagnosed peripheral arterial disease (PAD). Arterial ulcers typically result from PAD, either macro- or microvascular disease, which can be a result of arteriosclerosis or atherosclerosis. Progressive narrowing of the vessels manifests as poor circulation, decreasing the delivery of oxygen and nutrients to tissues while simultaneously preventing the removal of metabolic waste products, both of which contribute to delayed healing.[84] Ischemic pain, a major problem with severe PAD and possibly with an arterial ulcer, further debilitates the individual. See Chapter 4, Vascular Wounds, for a detailed discussion of diagnosis and treatment of PAD.

Other less common diseases that also cause arterial insufficiency with decreased oxygen perfusion of distal injured tissue, include but are not limited to the following: large and medium vessel disease as a result of arteriosclerosis obliterans, thromboangitis obliterans, arteriovenous malformation, Raynaud's phenomenon (microthrombotic disease), antiphospholipid syndrome, cholesterol emboli, Takayasu arteritis, sickle cell anemia and polycythemia vera, and acute trauma or previous lower extremity fracture.[85] The reduction in arterial blood supply results in tissue hypoxia and ischemic damage.[86] (Refer to Chapter 4.)

Risk factors for the development of atherosclerosis, a common cause of arterial insufficiency, include increasing age, smoking, hypertension, dyslipidemia, family history, diabetes, sedentary lifestyle, and obesity. Obesity, although associated with atherosclerosis, has not been directly correlated to arterial ulcers or insufficiency.[67] Further complicating the clinical picture is the fact that arterial insufficiency may be present in concert with other pathological conditions, which must be ruled out or addressed in tandem. Unlike venous ulcers that can be successfully treated with therapeutic compression, chronic wounds caused by arterial insufficiency require the restoration of arterial function via revascularization.[87]

Chronic Edema

Patients with chronic venous insufficiency suffer from ambulatory venous hypertension, meaning that the venous pressure remains elevated during ambulation.[88,89] The mechanism by which the sustained ambulatory venous hypertension causes ulcers remains unclear. Proposed theories include pericapillary fibrin cuff deposition, abnormalities of the fibrinolytic system, trapping of growth factors by macromolecules in the dermis,[90] an increase in the percentage of local senescent cells,[35] and leukocyte plugging in lower extremity vessels.[91] Ineffective pumping of the calf muscle combined with venous valve dysfunction or incompetence contributes to pooling of the blood in the dependent venous circulatory system. This triggers capillary damage and activates the inflammatory process implicated in the theory of leukocyte-mediated endothelial damage and cuffing.[92] The accumulation of fibrin itself has direct negative effects on wound healing by down-regulating the synthesis of collagen.[93] In addition, the presence of fibrin cuffing creates a barrier to normal vessel function and traps blood-derived growth factors.[94,95]

Chronic venous insufficiency is discussed in Chapter 4 and lymphedema, in Chapter 5. In addition to wounds developing specifically as a result of these pathologies, wounds of other etiologies will have slower or halted healing rates if edema is present. Frequently, if there is ankle hypomobility with resulting lower leg muscle atrophy, edema is undetected based on apparent girth (**FIGURE 11-17**). Performing the pitting test (pressing on the tissue with the forefinger for 5 seconds and watching for poor tissue rebounding) will detect edema. Even if the wound is not related to the edema (eg, trauma or pressure), management of the edema is a necessary component of the care plan in order to optimize healing. When cellular debris and necrotic cells are trapped in the interstitial spaces and healing tissue is further from the arterial supply, delayed wound healing affects return to optimal function.

FIGURE 11-17

A. Effect of edema on wound healing Edema impedes healing of a wound regardless of etiology. This patient received extensive debridement of skin and subcutaneous tissue for necrotizing fasciitis, followed by extensive skin grafts. The ankle had less than 30° range of motion, combined with trauma to the lymphatic system. Compression was a vital component of the care plan in order for the skin graft to fully heal. **B.** Healed skin graft.

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Cardiac Disease

The overall physical status of an organism, broadly defined as health and viability, is completely defined by the relative representation of cells in the five major categories set forth by a very comprehensive review by Haines et al.[35] The five categories are as follows:

1. Regenerative mitotic (stem) cells
2. Quiescent post-mitotic cells
3. Transformed cells (cancers)
4. Senescent post-mitotic cells
5. Apoptotic cells

Senescent post-mitotic cells are defined as cells that are damaged in ways that disable their ability to proliferate but do not cause carcinogenic transformation. Apoptotic cells are defined as cells that execute a normal death program. Perhaps one of the most sensitive tissue types to a balanced cell homeostasis is the cardiac tissue. Cardiac cells, termed cardiomyocytes, in healthy individuals represent a cell population that has terminally differentiated and are in a healthy state, ready to perform their specific function.[96]

Case Study

Although the lower extremity of Mr RG did not appear edematous, there was pitting with finger pressure and severe visible reflux upon standing more than 60 seconds. Vascular studies revealed incompetent valves in the greater saphenous vein; therefore, compression was initiated using a multilayer compression system with a decrease in calf girth of 1 cm at which time he was transitioned to a 40 mmHg, Class II compression garment.

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DISCUSSION QUESTIONS

1. What are the patient's risk factors for chronic venous insufficiency?
2. What mechanisms of edema interfere with this patient's ability to heal?

However, cardiac disease is a common comorbidity associated with poor wound healing. This may be a result of age or trauma-related tissue buildup of senescent cellular phenotypes, which creates cytotoxic local environments. The accumulation of senescent cell types over time is a major contributor to age-associated pathologies characterized by dysregulated inflammation, including atherosclerosis and stroke.[97,98]

A study by Zhao et al. in 2012 sought to determine the effect of type 2 diabetes on the reparative function of endothelial progenitor cells (EPCs), which are responsible for maintaining microvascular integrity and angiogenesis.[99] They hypothesized that the elevated hemoglobin A1C levels found in patients with diabetes have a profound effect on both peripheral and cardiovascular systems. The lack of EPCs at a site requiring vascular repair results in delayed healing, increased fibrosis, and an overall decrease in tissue function.

Clinically, patients with a cardiovascular system that is repeatedly insulted by prolonged exposure to elevated proinflammatory stressors, including obesity and elevated blood glucose levels, are at risk for delayed wound healing. Obesity is a common denominator in both cardiac disease and diabetes. Adipokines, produced by the adipose tissue, are in and of themselves proinflammatory. Thus, the overall proinflammatory bias impairs cardiac function and contributes to an overall systemic state of chronic inflammation, which has the potential to delay wound healing.[97,100,101]

Clinically, poor healing is observed in infection and dehiscence of postsurgical incisions and in distal lower extremity wounds of patients who have wounds of other etiologies (eg, pressure) that do not heal because of poor cardiac output (**FIGURE 11-18A, B**). This reinforces the importance of performing a complete systems review, including the cardiovascular system, for a patient who has a chronic, non-healing wound of any etiology.

FIGURE 11-18

A and B. Wounds with cardiac insufficiency Both of the ankle wounds were on patients whose healing potential was impaired by cardiac insufficiency. The wound in A was a 90-year-old lady with a known history that included coronary bypass surgery, mitral valve regurgitation, and pacemaker. The wound in B was on the ankle of a 65-year-old man who had no known history of heart disease. He had palpable pulses so the wound was thought to be more venous. However, after he had emergency cardiac bypass surgery, the wound healed in a timely sequence. Note that both wounds, while at first appearing to be venous by location, are actually on the ankle and not in the gaiter area. Also, the round even edges are typical of wounds that have hypoxia.

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CANCER/RADIATION

Three factors affect wound healing in patients who are being treated for any type of cancer: use of radiation to target specific malignant cells, use of chemotherapy to treat or prevent metastasis, and overall decline in general health when a patient is in a catabolic state.

Radiation

Radiotherapy is the use of ionizing radiation given as daily fractions over a period of weeks to a field that includes the tumor tissue and the

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surrounding nodal stations.[102] While every effort is made to target only the malignant cells, damage to adjacent tissue cannot always be avoided. The effects of the radiation on the tissue can be immediate, acute, and chronic and are summarized in **TABLE 11-12**.[103,104] In addition to causing wounds, which are much like partial- and full-thickness burns, wounds that occur long after the radiation has been discontinued (eg, trauma, pressure, neuropathic) will have impaired healing because of the histological changes that occur at the time of radiation.

TABLE 11-12

Immediate, Acute, and Chronic Effects of Radiation

Immediate (within 1 week)	Acute (days to weeks)	Chronic (months to years)
• Transient, faint erythema • Dilated capillaries • Epilation • Dry skin	• Erythema localized to radiation field • Warm and tender skin • Edema • Arteriole obstruction by fibrin thrombi • Small foci of hemorrhage • Hyperpigmentation • Dry desquamation • Wet desquamation • Ulceration	• Thin, dry, semitranslucent skin • Lack of hair follicles and sebaceous glands • Fibrosis of the skin • Dyspigmentation • Induration with loss of range of motion • Accumulation of fibrinous exudate under the skin • Telangiectasia • Delayed ulceration due to ischemia • Radionecrosis

The effects of radiation on the tissue are dependent on the following factors: dose, treatment volume, daily fraction size, energy and type of radiation, total treatment time, individual cellular differences, and host overall well-being.[105] Dosage is measured in mGrays. (One Gray is defined as the absorption of 1 joule of radiation energy by 1 kilogram of matter.) With low doses (up to 100 mGy) there may be single-strand DNA breaks in the cell; however, because of remaining DNA strands in the surrounding area, the damage may be repaired.[106] When medium doses (0.5–5 Gy) are used, cellular death occurs after one or more reproductive divisions as a result of irreparable double-strand DNA breaks. If more than 5 Gy are used, cellular death occurs immediately. The edema and occlusion of the small vessels prevent the influx of platelets to the injured tissue,[106] followed by an increased expression of matrix metalloproteinases, reduction in cytokines and fibroblast recruitment, and decreased angiogenesis.[102] Radiation also causes direct cell death to fibroblasts, which results in decreased tensile strength, altered collagen function, loss of normal tissue construction, and impaired wound healing. The lack of angiogenesis causes skin changes (eg, thin translucent appearance; absent hair follicles, ergo fewer stem cells; lower tensile strength), as well as poor healing of skin that is injured by trauma even after the radiation wound has resolved.[102]

Two therapies that have been reported as potentially beneficial for healing late radiation tissue injury include hyperbaric oxygen therapy[107,108] and stem cell therapy.[109,110] The purpose of both therapies is to increase tissue oxygenation with resulting revascularization of the injured tissue and thereby improve wound healing. As discussed in the case study, hair follicle transplants or pinch grafts have been used to replace hair follicles for dermal wounds occurring in skin damaged by radiation; the follicle bulges are a source of autologous stem cells. Treatment of radiation wounds is much like the treatment of superficial- and deep-partial thickness burns (see Chapter 10, Burn Wound Management): manage the drainage with absorbent dressings, remove necrotic tissue in the least painful way for the patient, prevent infection, use non-adherent dressings such as silicone-backed foams, and optimize quality of life during a very difficult time for the patient.

Chemotherapy

Like radiation, chemotherapy is intended to kill the cancer cells by interfering with cell division as a result of the chemical interaction with the DNA.[111] And like radiation, in the process chemotherapy also affects some of the normal cells. One of the most common systemic effects is myelosuppression, defined as decreased production of blood cells by the bone marrow. Myelosuppression results in three conditions that affect wound healing: anemia (decreased red blood cells) with fewer cells to deliver oxygen and nutrients to the injured tissue, neutropenia (decreased white blood cells, especially neutrophils) with decreased ability to phagocytose bacteria and increased risk for infection, and thrombocytopenia (decreased platelets) with an increased risk of bleeding. Chemotherapy has also been reported to inhibit protein synthesis, decrease angiogenesis, decrease extracellular matrix formation, and ultimately delay surgical wound healing or impede healing in other wounds such as pressure ulcers.

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Chemotherapy-induced peripheral neuropathy (CIPN) is a side effect of chemotherapy treatment that can potentially result in neuropathic wounds or prevent a patient with a plantar foot wound from feeling the causative mechanical forces. CIPN can be either sensory and painful or sensorimotor, and is often associated with nerve damage from diabetes, alcohol, or inherited neuropathy.[112]

Common categories of chemotherapeutic agents and their effects on wound healing are presented in **TABLE 11-13**.[90] The optimal time to deliver chemotherapy to patients requiring surgical removal of a tumor has been the focus of numerous human and animal studies. Historically it was felt that impaired wound healing occurred most commonly when drugs were administered preoperatively or within 3 weeks postoperatively (specifically those such as adriamycin[113]). In an extensive discussion of wound healing in patients with cancer, Payne et al.[81] conclude that "delaying the initiation of chemotherapeutic regimes until 7 to 10 days postoperatively seems to have minimal effects on wound healing in this patient population." However, the similarities of wound healing cellular processes and metastases of malignant cells are well-documented. Surgical removal of a tumor initiates the wound healing cascade in order to heal the incision; however, the inflammatory process that ensues involves cellular activity that forms "premetastatic niches" where tumor cells can successfully metastasize to and develop into tumors.[114,115] Both reviews conclude that postponing chemotherapy until after the surgical wound has healed may facilitate metastatic spread of cancer and that more studies are needed to determine the efficacy of pre- and perioperative chemotherapy.

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TABLE 11-13

Chemotherapies and Their Effects on Wound Healing

Chemotherapy Agents	Effect on Wound Healing	Recommendations
Alkylating agents Cyclophosphamide Chlorambucil Thiotepa Mechlorethamine Cisplatin	Inhibits fibroblast function Attenuates vasodilation and later neovascularization Delayed wound closure Decreased wound tensile strength	Use as low a dose as possible during the wound healing process
Antimetabolites Methotrexate 5-fluorouracil 6-mercaptopurine Azathioprine	Decrease in wound tensile strength especially in days 3–7	Administer leucovorin with methotrexate Optimize nutrition Begin administering drug 1–2 weeks postoperatively
Plant alkaloids Vincristine Vinblastine	Transient early decrease in wound tensile strength	Administer preoperatively
Antitumor antibiotics Cleomycin Doxorubicin Actinomycin D Mitomycin C	Limits skin fibroblast production with delayed closure Decreased wound tensile strength	Delay administration 1–2 weeks postoperatively

Adapted from Payne WG, Naidu DK, Wheeler CK, Barkoe D, Mentis M, Salas RE, Smith DJ, Robson MC. Wound healing in patients with cancer. *ePlasty*. 2008;e9. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/pmc2206003. Accessed September 1, 2018.

Bevacizumab, a frequently used chemotherapeutic agent, is an antiangiogenesis drug that works by targeting vascular endothelial growth factor (VEGF). Tumors require high vascularity for survival, so by decreasing the blood supply, tumor growth is impeded. However, wound healing (eg, incisions or pressure ulcers) may also be impaired. The effects of chemotherapy on wound healing are sometimes considered in the sequence of cancer interventions.[116,117] For example, if a patient has radiation for a tumor, followed by surgery to remove the residual malignant tissue, chemotherapy may be delayed until after the surgical incision has healed. If a patient has an existing wound, for example, a pressure ulcer, chemotherapy may be delayed until the wound is healed. Optimizing the healing response for the overall benefit of treating the cancer requires a team approach, including patient engagement and adherence.

Decline in General Health

Short-term systemic side effects of cancer treatments discussed above include nausea and vomiting with decreased appetite, which in turn may lead to protein and calorie deficits for wound healing. Fatigue, depression, stress, and an overall decline in medical status are complications of dealing with cancer and may factor into poor wound healing.

CASE STUDY

CONCLUSION

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Although it was obvious that the patient's tissue had been irradiated (note the lack of hair on the periwound skin), it had been years since the treatment; however, the ability of the epithelial cells to replicate was destroyed. Because the wound did granulate and the edges were flat, electrical stimulation was initiated using high-volt pulsed current, 100 pps, voltage sufficient to elicit a tingling response, and a positive active electrode (to attract epithelial cells). Although the response was slow, the wound did thinly epithelialize but would degenerate easily with the least amount of friction or edema.

The patient ultimately had dermatology intervention of transplanted hair follicles. Eight of the 32 transplanted follicles survived and were sufficient to enable the wound to fully epithelialize. The patient continued electrical stimulation at home and the wound remained closed. The key to success in this case was the patient's willingness to adhere to an intensive and changing care plan (**FIGURE 11-19**).

FIGURE 11-19

A. Case study wound, closed and remodeling

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AUTOIMMUNE DISORDERS

Autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and polyarteritis nodosa present a conundrum in medical management of associated wounds. The fluctuating state of inflammation of multiple organs, including small vessels to the skin, results in painful vasculitic wounds that are difficult to heal (**FIGURE 11-20**). Frequently, the patient is on steroid therapy to manage the systemic disorder, which may compromise the healing potential. However, if the inflammation is not controlled by medications, pain and wounding may progress.[118] Working closely with the rheumatologist who is managing the medications is required, especially in the acute phase.

FIGURE 11-20

Wound associated with autoimmune disorder Spontaneous wounds can occur on patients with autoimmune disorders, such as this one on the foot of a patient with systemic lupus erythematosus. They have a vasculitic presentation with skin necrosis, exquisite pain, and very slow healing because of the medications (eg, prednisone, methotrexate, and other anti-inflammatories).

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STRESS

Stress, both physical and psychological, has been shown to have a deleterious effect on wound healing. Closely associated with the stress response are fear, pre-surgical stress,[119] chronic wound-related pain, anticipatory pain (eg, with dressing changes), and anxiety.[120] Regardless of the cause of the stress, the mechanism is the same—stress modulates the immune system function which impairs wound healing.[121] The primary connection between stress and wound healing involves the interactive effects of glucocorticoids (cortisol and corticosterone) with proinflammatory cytokines (interleukins and tumor necrosis factor-α).[122] The higher levels of cortisol and the diminished expression of proinflammatory cytokines have been shown to retard the initial inflammatory phase of healing.[119] In addition, the catecholamines, norepinephrine, and epinephrine released in response to stress result in vasoconstriction, decreased tissue perfusion, and decreased cellular response to injury.[123] This results in decreased fibroblasts and subsequent decreased granulation formation.

Strategies that help overcome the effect of stress on wound healing include education especially as it relates to anticipated pain, relaxation exercises, topical and systemic pain management, cognitive therapy that alters anxiety,[120] physical exercise[124], and social support.[119]

PSYCHOSOCIAL BEHAVIORS

Stress can lead to higher levels of anxiety and depression, as well as increasing the risk for negative health behaviors such as deprived sleep, poor

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nutrition, lack of exercise, smoking, and alcohol and drug abuse.[125] The effects of smoking and alcohol abuse on each of the phases of wound healing are listed in **TABLE 11-14**.

TABLE 11-14

Effects of Smoking and Alcohol Abuse on Wound Healing Phases

	Inflammation	Proliferation	Remodeling
Smoking	Impaired leukocyte activity Decreased macrophages Decreased neutrophil bactericidal activity Decreased IL-1 products Decreased phagocytosis of bacteria and debris Cytotoxicity of natural killer cells	Decreased fibroblast migration Decreased wound contraction Decreased epithelial regeneration Decreased extracellular production Increased proteases	
Alcohol abuse	Decreased neutrophil chemokines with decreased neutrophil infiltration Decreased IL-8 and TNF-α Decreased monocyte function Decreased macrophage response to microbes	Decreased endothelial cell response Decreased angiogenesis Increased tissue hypoxia Impaired cell signaling	Decreased production of Type 1 collagen Increased level of MMP-8 Degradation of epithelial ECM Decreased tensile strength of skin

Smoking

Smoking adversely affects healing by several mechanisms, resulting in delayed and longer healing times, increased risk of surgical site and chronic wound infections, increased skin necrosis, and increased incidence of dehiscence.[126–128] The primary effect of smoking is tissue hypoxia as a result of several mechanisms, including vasoconstriction.[129,130] As a result, cutaneous blood flow can be decreased by as much as 40%, thereby causing ischemia and impaired wound healing.[131] The vasoconstriction is caused by nicotine stimulating the sympathetic nervous system, resulting in the release of catecholamines that trigger peripheral vasoconstriction and decreased tissue perfusion.[130] Nicotine also decreases fibronolytic activity and augments platelet adhesiveness, thus increasing blood viscosity and further decreasing the delivery of oxygen to peripheral injured tissue.[125,130] Two other substances in cigarettes that affect tissue perfusion are carbon monoxide, which binds to hemoglobin and thereby decreases the oxygen content of blood, and hydrogen cyanide, which impairs cellular oxygen metabolism.[125,130] As a result of these cellular effects, patients who smoke are also more likely to have higher rates of atherosclerosis, cardiovascular disease, PAD, chronic pulmonary disorders, and cancer, all of which have an impact on healing.

With the increased use of e-cigarettes that vaporize liquid nitrogen, the effect of these products on wound healing has been reported as well, with the following conclusions:

- E-cigarettes affect fibroblast proliferation and migration.
- E-cigarettes cause an increase of apoptosis.
- E-cigarettes prolong wound healing times.
- The adverse effects of cigarette smoke are greater than those of e-cigarettes.[132–134]

Fortunately, smoking has a transient effect on the tissue microenvironment, and cessation can restore the microenvironment rapidly. Recommendations are cessation at least 4 weeks prior to surgery; longer periods of smoking cessation will decrease the incidence of wound

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complications.[135–138] Abstinence until a surgical site has healed or at least 2 weeks has also been recommended.[128] Short-term cessation of less than 4 weeks does not appear to reduce postoperative complications. In summary, cessation of smoking can reverse some of the effects on wound healing, and patient education is a vital part of treating smokers who have wounds of any etiology.

Alcohol Abuse

Heavy alcohol abuse is defined as more than 4 drinks/day or 14 drinks/week for males and more than 3 drinks/day or 7 drinks/week for females.[139] Patients who are alcohol abusers have higher rates of hospital-acquired infections and surgical site infections.[139] Alcohol intake has been shown to increase insulin resistance and result in higher blood glucose levels.[50] In addition, alcohol abusers have a higher risk for malnutrition as a result of poor eating habits (**FIGURE 11-21A, B**).

FIGURE 11-21

A. Wound associated with alcohol abuse Non-healing wound on the anterior shin of a 23-year-old male who sustained the injury playing recreational sports. The wound was treated with compression, non-contact low-frequency ultrasound, debridement, and collagen matrix dressings.

B. Eight weeks after initiation of treatment Although the wound has improved with the treatment, it is not what would be expected for a healthy, nondiabetic young male. This is a red flag of some inhibiting factor. Further discussion with the patient revealed a high alcohol intake, and once he eliminated the drinking, the wound closed and remained healed.

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Wound healing is inhibited in the inflammatory, proliferative, and remodeling phases by the mechanisms listed in **TABLE 11-14**. Studies have shown that acute ethanol intoxication, not just chronic abuse, has a detrimental effect on wound healing.[140,141] In summary, there is a decrease in the inflammatory and immune responses to injury that result in both delayed healing and increased risk of infection, a decrease in fibroblast migration and angiogenesis during the proliferation phase, and a decrease in Type 1 collagen production with a concurrent increase in protease activity during the remodeling phase, resulting in weaker extracellular matrix.[142] The clinical presentation will be slower healing with a tendency to recur with any mechanical force.

FOREIGN BODIES

Foreign bodies are detected by the body's immune system, thereby initiating or increasing an inflammatory state that can impede wound healing, cause granuloma formation, or increase infection risk. The foreign body may be an identifiable exogenous material or an endogenous material that has become altered in such a way that the body responds to it as a foreign body.[143] Examples include tattoo and cosmetic filler particles, biomaterials and synthetic materials associated with medical devices and prostheses,[144] foam remnants associated with negative pressure wound therapy,[145]

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suture materials,[146–148] infected orthopedic hardware, and objects as a result of trauma (eg, glass, nails, needles, metal shards). The latter is especially of concern in the neuropathic foot when the wound is in an area other than a bony weight-bearing surface. The histological sequence of a foreign body reaction and granuloma formation is composed of macrophages and foreign body giant cells and is the end-stage response of the inflammatory and wound healing response.[143,144] Signs and symptoms of a foreign body in a wound include the following:

1. Failure of the wound to achieve full closure
2. Persistent drainage from a residual wound opening
3. Consistent epithelial breakdown of a closed wound
4. Subcutaneous tenderness
5. Palpable subcutaneous nodule
6. Periwound erythema and edema
7. Pain with weight-bearing (in the neuropathic foot)

Radiography can detect a metal foreign body; however, ultrasonography is recommended for a nonradiopaque foreign body.[149] Surface markers, multiple-projection radiographs, wire grids, fluoroscopy, or stereotaxic devices are also helpful in locating the embedded foreign body.[150] Removal of the foreign body is advised if possible, considering patient risk factors, followed by standard wound care to facilitate timely closure.

SUMMARY

Wounds will heal in a timely sequence if the cellular and tissue environment is healthy; however, there are numerous intrinsic, extrinsic, and local factors that can alter that environment and impede the healing process. These factors are usually related to infection, nutrition, medications, other disease processes and necessary interventions, or psychosocial behaviors. Identification of these factors and addressing the implications as part of a comprehensive care plan are essential in order for wounds to progress through all the phases of healing.

REFERENCES

1. Murphy K, ed. Janeway's Immunobiology. 7th ed. New York, NY: Garland Science, Taylor & Francis Group, LLC; 2007.

2. Snyder RJ, Bohn G, Hanft J, et al. Wound biofilm: current perspectives and strategies on biofilm disruption and treatments. *Wounds*. 2017;29(6):S1–S17. [PubMed: 28682297]

3. Krahenbuhl JL, Adams LB. The role of the macrophage in resistance to the leprosy bacillus. *Immunol Ser*. 1994;60:281–302. [PubMed: 8251574]

4. Bates-Jensen B, Schultz G, Ovington LG. Management of exudate, biofilms, and infection. In: Sussman C, Bates-Jensen B, eds. *Wound Care: A Collaborative Practice Manual for Health Professionals*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2012:457–476.

5. Bibel DJ, Aly R, Bayles C, Strauss WG, Shinefield HR, Maibach HI. Competitive adherence as a mechanism of bacterial interference. *Can J Microbiol*. 1983;29(6):700–703. [PubMed: 6411317]

6. Collette JR, Lorenz MC. Mechanisms of immune evasion in fungal pathogens. *Curr Opin Microbiol*. 2011;14(6):668–675. [PubMed: 21955887]

7. Kuosjy BL. Infectious problems of the foot in diabetic patients. In: Fowker JH, Pfeifer MA, eds. *Levin & O'Neal's The Diabetic Foot*. 7th ed. Philadelphia, PA: Mosby/Elsevier; 2008:305–318.

8. Haalboom M, Blokhuis-Arkes MHE, Beuk RJ, et al. Wound swab and wound biopsy yield similar culture results. *Wound Repair Regen*. 2018. Available at: doi:10.1111/wrr.12629. Accessed August 28, 2018.

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9. Ehrlich HP, Hunt TK. Effects of cortisone and vitamin A on wound healing. *Ann Surg*. 1968;167(3):324–328. [PubMed: 5638517]

10. Ehrlich HP, Tarver H, Hunt TK. Effects of vitamin A and glucocorticoids upon inflammation and collagen synthesis. *Ann Surg*. 1973;177(2):222–227. [PubMed: 4572787]

11. Roberts AB. Transforming growth factor-beta: activity and efficacy in animal models of wound healing. *Wound Repair Regen*. 1995;3(4):408–418. [PubMed: 17147652]

12. Mueller RV, Hunt TK, Tokunaga A, Spencer EM. The effect of insulinlike growth factor I on wound healing variables and macrophages in rats. *Arch Surg*. 1994;129(3):262–265. [PubMed: 8129600]

13. Steenfos HH, Hunt TK, Scheuenstuhl H, Goodson WH 3rd. Selective effects of tumor necrosis factor-alpha on wound healing in rats. *Surgery*. 1989;106(2):171–175; discussion 175–176. [PubMed: 2763024]

14. Cerci C, Yildirim M, Ceyhan M, Bozkurt S, Doguc D, Gokicimen A. The effects of topical and systemic beta glucan administration on wound healing impaired by corticosteroids. *Wounds*. 2008;20:12. Available at: http://www.medscape.com/viewarticle/586467. Accessed May 1, 2013.

15. Khanna R, Dlouhy BJ, Smith ZA, Lam SK, Koski TR, Kahdaleh NS. The impact of steroids, methotrexate, and biologics on clinical and radiographic outcomes in patients with rheumatoid arthritis undergoing fusions at the craniovertebral junction. *J Craniovertebr Junction Spine*. 2015;6(2):60–64. [PubMed: 25972710]

16. Tada M, Inui K, Sugioka Y, et al. Delayed wound healing and postoperative surgical site infections in patients with rheumatoid arthritis treated with or without biological disease-modifying antirheumatic drugs. *Clin Rheumatol*. 2016;35(6):147581.

17. Ito H, Kijima M, Nishida K, et al. Postoperative complications in patients with rheumatoid arthritis using a biological agent—a systematic review and meta-analysis. *Mod Rheumatol*. 2015;25(5):672–678. [PubMed: 25671400]

18. Kubota A, Nakamura T, Miyazaki Y, Sekiguchi M, Suguro T. Perioperative complications in elective surgery in patients with rheumatoid arthritis treated with biologics. *Mod Rheumatol*. 2012;22(6):844–848. [PubMed: 22354636]

19. Tsai DM, Borah GL. Implications of rheumatic disease and biological response—modifying agents in plastic surgery. *Plast Reconstr Surg*. 2015;136(6):1327–1336. [PubMed: 26595025]

20. Gaucher S, Nicolas C, Piveteau O, Philippe H, Blanche P. Sarcoidosis and wound healing after cellulitis of the lower limb: is methotrexate responsible for skin graft failure? *Wounds*. 2017;29(8):229–230. [PubMed: 28862976]

21. Chakravarty K, McDonald H, Pullar T, et al. BSR/BHPR guideline for disease modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. *Rheumatology (Oxford)*. 2008;47(6):924–925. [PubMed: 16940305]

22. Ledingham J, Deighton C. Update on the British Society for Rheumatology guidelines for prescribing TNFα blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). *Rheumatology (Oxford)*. 2005;44(2):157–163. [PubMed: 15637039]

23. Busti AJ, Hooper JS, Amaya CJ, Kazi S. Effects of perioperative anti-inflammatory and immunomodulating therapy on surgical wound healing. *Pharmacotherapy*. 2005;25(11):1566–1591. [PubMed: 16232020]

24. Beitz JM. Pharmacologic impact (aka “breaking bad”) of medications on wound healing and wound development: a literature-based overview. *Ostomy Wound Manage*. 2017;63(3):18–35.

25. Fairweather M, Heit YI, Rosenberg LM, Briggs A, Orgill DP, Bertagnoli MM. Celecoxib inhibits early cutaneous wound healing. *J Surg Res*. 2015;194(2):717–724. [PubMed: 25588948]

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26. Patrono C. The multifaceted clinical read-outs of platelet inhibition by low-dose aspirin. *J Am Coll Cardiol*. 2015;66(1):74–85. [PubMed: 26139061]

27. Pasero C, Stannard D. The role of intravenous acetaminophen in acute pain management. *Pain Manag Nurs*. 2012;13(2):107–124. [PubMed: 22652283]

28. Kragh AM, Walden M, Apelqvist A, Wagner P, Atroshi I. Bleeding and first-year mortality following hip fracture surgery and preoperative use of low-dose acetylsalicylic acid. *BMC Musculoskelet Disord*. 2011;12(254). Available at: http://www.medscape.com/viewarticle/757643. Accessed June 23, 2013.

29. Levine JM. The effect of oral medication on wound healing. *Adv Skin Wound Care*. 2017;30(3):137–142. [PubMed: 28198745]

30. Limmer JS, Grotegut CA, Thames E, Dotters-Katz SK, Brancazio LR, James AH. Postpartum wound and bleeding complications in women who received peripartum anticoagulation. *Thromb Res*. 2013;132(1):e19–e23. [PubMed: 23735589]

31. Choudhry S, Fishman PM, Hernandez C. Heparin-induced bullous hemorrhagic dermatosis. *Cutis*. 2013;91(2):93–9. [PubMed: 23513558]

32. Amato L, Berti S, Fabbri P. Warfarin-induced skin necrosis. Available at: http://medscape.com/viewarticle/451073_2. Accessed May 7, 2017.

33. Smith SL. Immunosuppressive therapies in organ transplantation. Available at: http://www.medscape.com/viewarticle437182. Accessed June 3, 2013.

34. Smith SI. Immunosuppressive therapies in organ transplantation. Available at: http://medscape.com/viewarticle437182. Accessed May 7, 2017.

35. Haines DD, Juhasz B, Tosaki A. Management of multicellular senescence and oxidative stress. *J Cell Mol Med*. 2013;17(8):936-957.

36. Francis S, Berg D. Reducing skin malignancy in organ transplant recipients. *Skin Therapy Lett*. 2013;18(1). Available at: http://www.medscape.com/viewarticle/777623. Accessed May 3, 2013.

37. Hunt SA, Haddad F. The changing face of heart transplantation. *J Am Coll Cardiol*. 2008;52(8):587–598. [PubMed: 18702960]

38. Singer AJ, Clark RA. Cutaneous wound healing. *N Engl J Med*. 1999;341(10):738–746. [PubMed: 10471461]

39. Genco RJ, Grossi SG, Ho A, Nishimura F, Murayama Y. A proposed model linking inflammation to obesity, diabetes, and periodontal infections. *J Periodontol*. 2005;76(11 suppl):2075–2084.

40. Wetzler C, Kampfer H, Stallmeyer B, Pfeilschifter J, Frank S. Large and sustained induction of chemokines during impaired wound healing in the genetically diabetic mouse: prolonged persistence of neutrophils and macrophages during the late phase of repair. *J Invest Dermatol*. 2000;115(2):245–253. [PubMed: 10951242]

41. Wong SL, Demers M, Martinod K, et al. Diabetes primes neutrophils to undergo NETosis which severely impairs wound healing. *Nat Med*. 2015;21(7):815–819. [PubMed: 26076037]

42. Loots MA, Lamme EN, Zeegelaar J, Mekkes JR, Bos JD, Middelkoop E. Differences in cellular infiltrate and extracellular matrix of chronic diabetic and venous ulcers versus acute wounds. *J Invest Dermatol*. 1998;111(5):850–857. [PubMed: 9804349]

43. Werner S, Krieg T, Smola H. Keratinocyte-fibroblast interactions in wound healing. *J Invest Dermatol*. 2007;127(5):998–1008. [PubMed: 17435785]

44. Werner S, Breeden M, Hubner G, Greenhalgh DG, Longaker MT. Induction of keratinocyte growth factor expression is reduced and delayed during wound healing in the genetically diabetic mouse. *J Invest Dermatol*. 1994;103(4):469–473. [PubMed: 7930669]

45. Liao H, Zakhaleva J, Chen W. Cells and tissue interactions with glycated collagen and their relevance to delayed diabetic wound healing.

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Biomaterials. 2009;30(9):1689–1696. [PubMed: 19157537]

46. Dalton SJ, Whiting CV, Bailey JR, Mitchell DC, Tarlton JF. Mechanisms of chronic skin ulceration linking lactate, transforming growth factor-beta, vascular endothelial growth factor, collagen remodeling, collagen stability, and defective angiogenesis. *J Invest Dermatol*. 2007;127(4):958–968. [PubMed: 17218944]

47. Ben-Porath I, Weinberg RA. The signals and pathways activating cellular senescence. *Int J Biochem Cell Biol*. 2005;37(5):961–976. [PubMed: 15743671]

48. Tchaikovski V, Olieslagers S, Bohmer FD, Waltenberger J. Diabetes mellitus activates signal transduction pathways resulting in vascular endothelial growth factor resistance of human monocytes. *Circulation*. 2009;120(2):150–159. [PubMed: 19564559]

49. American College of Endocrinology. Clinical Practice Guidelines for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient—2013 Update. Available at: https://www.aace.com/files/publish-ahead-of-print-final-version.pdf. Accessed May 4, 2013.

50. Markuson M, Hanson D, Anderson J, et al. The relationship between hemoglobin A1c values and healing time for lower extremity ulcers in individuals with diabetes. *Adv Skin Wound Care*. 2009;22(8):365–372. [PubMed: 19638800]

51. Joseph JI. Anesthesia and surgery in the diabetic patient. In: Goldstein BJ, Müller-Wieland D, eds. *Type 2 Diabetes: Principles and Practice*. 2nd ed. New York, NY: Informa Healthcare; 2008:475–500.

52. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. *Nat Rev Cardiol*. 2009;6(6):399–409. [PubMed: 19399028]

53. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*. 2006;444(7121):840–846. [PubMed: 17167471]

54. Kahn SE, Zinman B, Haffner SM, et al. Obesity is a major determinant of the association of C-reactive protein levels and the metabolic syndrome in type 2 diabetes. *Diabetes*. 2006;55(8):2357–2364. [PubMed: 16873701]

55. Sari N. Physical inactivity and its impact on healthcare utilization. *Health Econ*. 2009;18(8):885–901. [PubMed: 18792089]

56. Zajacova A, Dowd JB, Burgard SA. Overweight adults may have the lowest mortality—do they have the best health? *Am J Epidemiol*. 2011;173(4):430–437. [PubMed: 21228416]

57. Lee MJ, Wu Y, Fried SK. Adipose tissue remodeling in pathophysiology of obesity. *Curr Opin Clin Nutr Metab Care*. 2010;13(4):371–376. [PubMed: 20531178]

58. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol*. 2011;11(2):85–97. [PubMed: 21252989]

59. Pence BD, Woods JA. Exercise, obesity, and cutaneous wound healing: evidence from rodent and human studies. *Adv Wound Care*. 2014;3(1):71–79.

60. Allama A, Ibrahim I, Abdallah A, et al. Effect of body mass index on early clinical outcomes after cardiac surgery. *Asian Cardiovasc Thorac Ann*. 2014;22(6):667–673 47. [PubMed: 24887880]

61. Lemaignen A, Birgand G, Ghodhbane W, et al. Sternal wound infection after cardiac surgery: incidence and risk factors according to clinical presentation. *Clin Microbiol Infect*. 2015;21(7):674.e11–674.e18.

62. Stevens SM, O'Connell BP, Meyer TA. Obesity related complications in surgery. *Curr Opin Otolaryngol Head Neck Surg*. 2015;23(5):341–347. [PubMed: 26339964]

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63. Pierpont YN, Dinh TP, Salas RE, et al. Obesity and surgical wound healing: a current review. *ISRN Obes*. 2014:Article ID 638936.

64. Cottam DR, Mattar SG, Barinas-Mitchell E, et al. The chronic inflammatory hypothesis for the morbidity associated with morbid obesity: implications and effect of weight loss. *Obes Surg*. 2004;14(5):589–600. [PubMed: 15186624]

65. Khalil H, Cullen M, Chambers H, Carroll M, Walker J. Elements affecting wound healing time: an evidence based analysis. *Wound Repair Regen*. 2015;23(4):550–556. [PubMed: 25907979]

66. Breen L, Phillips SM. Skeletal muscle protein metabolism in the elderly: interventions to counteract the "anabolic resistance" of ageing. *Nutr Metab*. 2011;8(68). Available at: http://www.medscape.com/viewarticle/754680. Accessed June 23, 2013.

67. Frost KR. Use of steroids for wasting and lipodystrophy syndromes in HIV/AIDs. *AIDS Read*. 2001;11(3). Available at: http://www.medscape.com/viewarticle/410372. Accessed June 23, 2013.

68. Sam J, Nguyan GC. Protein-calorie malnutrition as a prognostic indicator of mortality among patients hospitalized with cirrhosis and portal hypertension. *Liver Int*. 2009;29(9):1396–1402. [PubMed: 19602136]

69. Demling RH. Nutrition, anabolism, and the wound healing process: an overview. *ePlasty*. 2009;9:65–94.

70. Patterson GK, Martindate RG. Nutrition and wound healing. In: McCulloch JM, Kloth LC, eds. *Wound Healing: Evidence-Based Medicine*. 4th ed. Philadelphia, PA: FA Davis Company; 2010:44–50.

71. Huckleberry Y. Nutritional support and the surgical patient. *Am J Health Syst Pharm*. 2004:61(7). Available at: http://www.medscape.com/viewarticle/474066_6. Accessed June 25, 2013.

72. Parrish CR. Serum proteins as markers of nutrition: what are we treating? *Pract Gastroenterol*. 2006;October:46–64. Available at: http://www.medicine.virginia.edu/clinical/departments/medicine/divisions/digestive-health/nutrition-support-team/nutrition-articles/BanhArticle.pdf. Accessed September 25, 2014.

73. Baeten JM, Richardson BA, Bankson DD, et al. Use of serum retinol-binding protein for prediction of vitamin A deficiency: effects of HIV-1 infection, protein malnutrition, and the acute phase response. *Am J Clin Nutr*. 2004;79(2):218–225. [PubMed: 14749226]

74. Quain AM, Khardori NM. Nutrition in wound care management: a comprehensive overview. *Wounds*. 2015;27(12):327–335. [PubMed: 27447105]

75. Collins N, Friedrich L. Appropriately diagnosing malnutrition to improve wound healing. *Wound Clin*. 2016;10(11):10–12.

76. Laporte M. The Canadian Nutrition Screening Tool. *Adv Skin Wound Care*. 2017;30(2):64–65. [PubMed: 28106633]

77. Fulton J, Evans B, Miller S, et al. Development of a nutrition screening tool for an outpatient wound center. *Adv Skin Wound Care*. 2016;29(3):136–142. [PubMed: 26866870]

78. Kaiser MJ, Bauer JM, Ramsch C, et al. Validation of the mini nutritional assessment short-form (MNA®-SF): a practical tool for identification of nutritional status. *J Nutr Health Aging*. 2009;13:782–788. [PubMed: 19812868]

79. Wu G, Bazer FW, Davis TA, et al. Arginine metabolism and nutrition in growth, health, and disease. *Amino Acids*. 2009;37(1):153–168. [PubMed: 19030957]

80. Leigh B, Desneves K, Rafferty J, et al. The effect of different doses of arginine-containing supplement on the healing of pressure ulcers. *J Wound Care*. 2012;21(3):150–156. [PubMed: 22399084]

81. Payne WG, Naidu DK, Wheeler CK, et al. Wound healing in patients with cancer. *ePlasty*. 2008;8:e9. Available at:

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https://www.medscape.com/medline/abstract/18264518. Accessed September 1, 2018. [PubMed: 18264518]

82. Hourigan LA, Omaye ST, Keen CL, Jones JA, Dubick MA. Vitamin and trace element loss from negative-pressure wound therapy. *Adv Skin Wound Care*. 2016;29(1):20–25. [PubMed: 26650093]

83. Bolton L. Evidence corner. *Wounds*. 2017;29(10):324–326.

84. Werdin F, Tennenhaus M, Schaller HE, Rennekampff HO. Evidence-based management strategies for treatment of chronic wounds. *ePlasty*. 2009;9:e19. [PubMed: 19578487]

85. Hess CT. Arterial ulcer checklist. *Adv Skin Wound Care*. 2010;23(9):432. [PubMed: 20729649]

86. Grey JE, Harding KG, Enoch S. Venous and arterial leg ulcers. *BMJ*. 2006;332(7537):347–350. [PubMed: 16470058]

87. Hopf HW, Ueno C, Aslam R, et al. Guidelines for the treatment of arterial insufficiency ulcers. *Wound Repair Regen*. 2006;14(6):693–710. [PubMed: 17199834]

88. Bergan JJ, Schmid-Schonbein GW, Coleridge PD, Nicolaides AN, Boisseau MR, Eklof B. Chronic venous disease. *NEJM*. 2006;355:488–498. [PubMed: 16885552]

89. de Araujo T, Valencia I, Federman DG, Kirsner RS. Managing the patient with venous ulcers. *Ann Intern Med*. 2003;138(4):326–334. [PubMed: 12585831]

90. Falanga V, Eaglstein WH. The “trap” hypothesis of venous ulceration. *Lancet*. 1993;341(8851):1006–1008. [PubMed: 7682272]

91. Browse NL, Burnand KG. The cause of venous ulceration. *Lancet*. 1982;2(8292):243–245. [PubMed: 6124673]

92. Collins L, Seraj S. Diagnosis and treatment of venous ulcers. *Am Fam Physician*. 2010;81(8):989–996. [PubMed: 20387775]

93. Pardes JB, Takagi H, Martin TA, Ochoa MS, Falanga V. Decreased levels of alpha 1(I) procollagen mRNA in dermal fibroblasts grown on fibrin gels and in response to fibrinopeptide B. *J Cell Physiol*. 1995;162(1):9–14. [PubMed: 7814454]

94. Higley HR, Ksander GA, Gerhardt CO, Falanga V. Extravasation of macromolecules and possible trapping of transforming growth factor-beta in venous ulceration. *Br J Dermatol*. 1995;132(1):79–85. [PubMed: 7538779]

95. Kobrin KL, Thompson PJ, van de Scheur M, Kwak TH, Kim S, Falanga V. Evaluation of dermal pericapillary fibrin cuffs in venous ulceration using confocal microscopy. *Wound Repair Regen*. 2008;16(4):503–506. [PubMed: 18638268]

96. Herrup K, Yang Y. Cell cycle regulation in the postmitotic neuron: oxymoron or new biology? *Nat Rev Neurosci*. 2007;8(5):368–378. [PubMed: 17453017]

97. Buckley CD, Gilroy DW, Serhan CN, Stockinger B, Tak PP. The resolution of inflammation. *Nat Rev Immunol*. 2012;12(1):3.

98. Rocha VZ, Libby P. Obesity, inflammation and atherosclerosis. *Nat Rev Cardiol*. 2009;6(6):399–409. [PubMed: 19399028]

99. Zhao CT, Wang M, Siu CW, et al. Myocardial dysfunction in patients with type 2 diabetes mellitus: role of endothelial progenitor cells and oxidative stress. *Cardiovasc Diabetol*. 2012;11:147. [PubMed: 23217199]

100. Abrahamian H, Endler G, Exner M, et al. Association of low-grade inflammation with nephropathy in type 2 diabetic patients: role of elevated CRP-levels and 2 different gene-polymorphisms of proinflammatory cytokines. *Exp Clin Endocrinol Diabetes*. 2007;115(1):38–41. [PubMed: 17286233]

101. Ouchi N, Walsh K. A novel role for adiponectin in the regulation of inflammation. *Arterioscler Thromb Vasc Biol*. 2008;28(7):1219–1221. [PubMed:

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18565846]

102. Subramania I, Balasubramanian D. Management of radiation wounds. *Indian J Plast Surg*. 2012;45(2):325–331. [PubMed: 23162232]

103. Mendelsohn FA, Divino CM, Reis ED, Kerstein MD. Wound care after radiation therapy. *Adv Skin Wound Care*. 2002;15(5):216–224. [PubMed: 12368711]

104. Haubner F, Ohmann E, Pohl F, Strutz J, Gassner HG. Wound healing after radiation therapy: review of the literature. *Radiat Oncol*. 2012;7:162–170. [PubMed: 23006548]

105. Gosselin TK, Schneider SM, Plambeck MA, Rowe K. A prospective randomized, placebo-controlled skin care study in women diagnosed with breast cancer undergoing radiation therapy. *Oncol Nurs Forum*. 2010;37(5):619–626. [PubMed: 20797953]

106. Tibbs MK. Wound healing following radiation therapy: a review. *Radiother Oncol*. 1997;42:99–106. [PubMed: 9106919]

107. Bennett MH, Feldmeier J, Hampson NB, Smee R, Milross C. Hyperbaric oxygen therapy for late radiation tissue injury. *Cochrane Database Syst Rev*. 2016;4:CD0050555.

108. Borab Z, Mirmanesh MD, Gantz M, Cusano A, Pu LL. Systematic review of hyperbaric oxygen therapy for the treatment of radiation-induced skin necrosis. *J Plast Reconstr Aesthet Surg*. 2017;70(4):529–538. [PubMed: 28081957]

109. Benderitter M, Caviggioli F, Chapel A, et al. Stem cell therapies for the treatment of radiation-induced normal tissue side effects. *Antioxid Redox Signal*. 2014;21(2):338–355.

110. Rigotti G, Marchi A, Varoni GM, et al. Clinical treatment of radiotherapy tissue damage by lipoaspirate transplant: a healing process mediated by adipose-derived adult stem cells. *Plast Reconstr Surg*. 2007;119(5):1409–1422. [PubMed: 17415234]

111. Goodman CC, Snyder TE. Problems affecting multiple systems. In: Goodman CC, Fuller KS, Boissonnault WG., eds. *Pathology: Implications for Physical Therapists*. Philadelphia, PA: Saunders. 2003;85–119.

112. Quasthoff S, Hartung HP. Chemotherapy-induced peripheral neuropathy. *J Neurol*. 2002;249(1):9–17. [PubMed: 11954874]

113. Guo S, DiPietro LA. Factors affecting wound healing. *J Dent Res*. 2010;89(3):219–229. [PubMed: 20139336]

114. Harless WH. Revisiting perioperative chemotherapy: the critical importance of targeting residual cancer prior to wound healing. *BMC Cancer*. 2009;9(118). Available at: https://doi-org.ezproxy.cihe.edu.hk/10.1186/1471-2407-9-118. Accessed September 1, 2018.

115. Celeen W, Pattyn P, Marell M. Surgery, wound healing, and metastasis: recent insights and clinical implications. *Crit Rev Oncol Hematol*. 2013;89(1):16–26. [PubMed: 23958676]

116. Gordon CR, Rojavin Y, Patel M, et al. A review of bevacizumab and surgical wound healing: an important warning to all surgeons. *Ann Plast Surg*. 2009;62(6):707–709. [PubMed: 19461291]

117. Erinjeri JP, Fong AJ, Kemeny NE, Brown KT, Getrajdman GI, Solomon SB. Timing of administration of bevacizumab chemotherapy affects wound healing after chest wall port placement. *Cancer*. 2011;117(6):1296–1301. [PubMed: 21381016]

118. Padovan M, Vincenzi F, Govoni M, et al. Adenosine and adenosine receptors in rheumatoid arthritis. *Int J Clin Rheumatol*. 2013;8(1):13–25.

119. Gouin JP, Kiecolt-Glaser JK. The impact of psychological stress on wound healing: methods and mechanisms. *Immunol Allergy Clin North Am*. 2011;31(1):81–93. [PubMed: 21094925]

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120. Woo K. Exploring the effects of pain and stress on wound healing. *Adv Skin Wound Care*. 2012;25(1):38–44. [PubMed: 22218069]

121. Lucas VS. Psychological stress and wound healing in humans. *Wounds*. 2011;22(4):76–83.

122. Christian LM, Graham JE, Pdgett DA, Glser R, Keicolt-Glaser JK. Stress and wound healing. *Neuroimmunomodulation*. 2006:13(5–6):337–346. [PubMed: 17709956]

123. Ennis WJ, Meneses P. Complications in repair. In: McCulloch JM, Kloth LC, eds. *Wound Healing: Evidence-Based Medicine*. 4th ed. Philadelphia, PA: FA Davis Company; 2010:51–64.

124. Saguie BO, Romana-Souza B, Martins RL, Monte-Alto-Costa A. Exercise prior to, but not concomitant with, stress reverses stress-induced delayed skin wound healing. *Wound Repair Regen*. 2017;25(4):641–651. [PubMed: 28628259]

125. Guo S, DiPietro LA. Factors affecting wound healing. *J Dent Res*. 2010;89(3):219–229. [PubMed: 20139336]

126. Theocharidis V, Katsaros I, Sgouromallis E, et al. Current evidence on the role of smoking in plastic surgery elective procedures: a systematic review and meta-analysis. *J Plast Reconstr Aesthet Surg*. 2018;71(5):624–636. [PubMed: 29426809]

127. Sorensen, LT. Wound healing and infection in surgery. The clinical impact of smoking and smoking cessation: a systematic review and meta-analysis. *Arch Surg*. 2012;147(4):373–383. [PubMed: 22508785]

128. Pluvy I, Panouilleres M, Garrido I, et al. Smoking and plastic surgery, part II. Clinical implications: a systematic review with meta-analysis. *Ann Chir Plast Esthet*. 2015;60(1):e15–e49. [PubMed: 25447218]

129. Basnett AM. Cutaneous manifestations of smoking. 2018. Available at: http://emedicine.medscape.com/article/1075039. Accessed September 2, 2018.

130. McDaniel JC, Browning KK. Smoking, chronic wound healing, and implications for evidence-based practice. *J Wound Ostomy Continence Nurs*. 2014;41(5):415–423; quiz E1–E2. [PubMed: 25188797]

131. Sorensen LT. Smoking and wound healing. *Eur Wound Manage Assoc J*. 2003;3:13–15.

132. Alanazi H, Park HJ, Chakir J, Semlali A, Rouabhia M. Comparative study of the effects of cigarette smoke and electronic cigarettes on human gingival fibroblast proliferation, migration, and apoptosis. *Food Chem Toxicol*. 2018;118:390–398. [PubMed: 29800583]

133. Taub PJ, Matarasso A. E-cigarettes and potential implications for plastic surgery. *Plast Reconstr Surg*. 2016;138(6):1059e–1066e. [PubMed: 27879608]

134. Agochukwu N, Liau JY. Debunking the myth of e-cigarettes: a case of free flap compromise due to e-cigarette use within the first 24 hours. *J Plast Reconstr Aesthet Surg*. 2018;71(3):451–453. [PubMed: 29031575]

135. Sorensen LT. Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review. *Ann Surg*. 2012;255(6):1069–1079. [PubMed: 22566015]

136. Sorensen LT. Wound healing and infection in surgery. The clinical impact of smoking and smoking cessation: a systematic review and meta-analysis. *Arch Surg*. 2012;147(4):373–383. [PubMed: 22508785]

137. Mills E, Eyawo O, Lockhrt I, Kelly S, Wu P, Ebbert JO. Smoking cessation reduces postoperative complications: a systematic review and meta-analysis. *Am J Med*. 2011;124(2):144–154. [PubMed: 21295194]

138. Wong J, Lam DP, Abrishami A, Chan MT, Chung F. Short-term preoperative smoking cessation and postoperative complications: a systematic

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review and meta-analysis. *Can J Anaesth*. 2012;59(3):268–279. [PubMed: 22187226]

139. deWit M, Goldberg S, Hussein E, Neifeld JP. Health care-associated infections in surgical patients undergoing elective surgery: are alcohol use disorders a risk factor? *J Am Coll Surg*. 2012;215:229–236. [PubMed: 22727411]

140. Ranzer MJ, Chen L, DiPietro LA. Fibroblast function and wound breaking strength is impaired by acute ethanol intoxication. *Alcohol Clin Exp Res*. 2011;35(1):83–90. [PubMed: 20958333]

141. Radek KA, Matthies AM, Burns AL, Heinrich SA, Kovacs EJ, DiPietro LA. Acute ethanol exposure impairs angiogenesis and the proliferative phase of wound healing. *Am J Physiol Heart Circ Physiol*. 2005; 289:H1084–H1090. [PubMed: 15863463]

142. Radek KA, Ranzer MJ, DiPietro LA. Brewing complications: the effect of acute ethanol exposure on wound healing. *J Leukoc Biol*. 2009;86:1125–1134. [PubMed: 19675208]

143. Molina-Ruiz AM, Requena L. Foreign body granulomas. *Dermatol Clin*. 2015;33:497–523. [PubMed: 26143429]

144. Anderson JM, Rodrigues A, Chang DT. Foreign body reaction to biomaterials. Available at: https://doi-org.ezproxy.cihe.edu.hk/10.1016/j.smim.2007.11.004. Accessed September 2, 2018.

145. Mazoch M, Montgomery C. Retained wound vacuum foam in non-healing wounds: a real possibility. *J Wound Care*. 2015;24(6 suppl):S18–S20. [PubMed: 26075511]

146. Chandorkar Y, Bhaskar N, Madras G, Basu B. Long-term sustained release of salicylic acid from cross-linked biodegradable polyester induces a reduced foreign body response in mice. *Biomacromolecules*. 2015;16(2):636–649. [PubMed: 25559641]

147. Lambertz A, Schroder KM, Schob DS, et al. Polyvinylidene fluoride as a suture material: evaluation of comet tail-like infiltrate and foreign body granuloma. *Eur Surg Res*. 2015;55(1–2):1–11.

148. Sung KY, Lee SY. A chronic, nonhealing wound of the finger caused by polypropylene suture material. *Wounds*. 2015;27(7):E16–E19. [PubMed: 26214386]

149. Turkcuer I, Atilla R, Topacoglu H, et al. Do we really need plain and soft-tissue radiographies to detect radiolucent foreign bodies in the ED? *Am J Emerg Med*. 2006;24(7):763–768. [PubMed: 17098094]

150. Lammers RL. Soft tissue foreign bodies. *Ann Emerg Med*. 1988;17(12):1336–1347. [PubMed: 3057951]

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